BIOLOGICS: THE NEW ANTITRUST FRONTIER

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The pharmaceutical industry lies at the intersection of patent law, antitrust law, federal and state regulations, and complex markets. For the past several decades, courts and commentators have analyzed issues presented by brand-name and generic drug companies in the "small molecule" setting. But just as they have begun to comprehend the multiple moving parts, a new frontier has arisen involving large molecules known as "biologics."

Biologics differ from small-molecule drugs along multiple axes. They are more expensive, costing hundreds of millions of dollars to develop. They cannot be precisely replicated, followed by "biosimilars" rather than generics. They are governed not by the Hatch-Waxman Act but by the Biologics Price Competition and Innovation Act. And they present a blank slate on which issues of innovation and competition will be hammered out in the decades to come. Given that biologics promise revolutionary advances like treatments for previously incurable diseases and cancer regimens offering substantial benefits over chemotherapy, the stakes could not be higher.

The small-molecule setting has been replete with collusive behavior such as "reverse payment" agreements by which brands and generics settle patent litigation and unilateral conduct by which brands modify their drugs to block generics, file frivolous government petitions, manipulate the regulatory regime, and deny materials generics need to enter the market. How likely are these (or other) forms of conduct to appear in the biologics industry? And if these behaviors occur, how should antitrust law respond? This Article addresses these questions, offering an antitrust framework for the conduct most likely to arise. In particular, it concludes that in the biologics setting, "citizen petitions," the disparagement of biosimilars, and collusion between biologics and biosimilars will be more frequent and that "product hopping" and reverse-payment settlements will be less typical. This Article also recommends utilizing an antitrust analysis similar to what courts have applied in the small-molecule setting and applying a modestly more deferential analysis for citizen petitions.

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Antitrust finds itself at a unique and crucial moment: poised at the precipice of a new industry but able to draw on decades of case law in an analogous setting that has addressed issues of competition and innovation. It is far from obvious how much courts can—or should—take from that setting. This Article assists in this task by determining which antitrust principles and doctrines should be exported to the biologics setting while appreciating the differences that counsel against such extrapolation. Given the importance of life-saving cancer treatments and an impending $400 billion market, there is no time to waste.

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I. INTRODUCTION

The pharmaceutical industry lies at the intersection of patent law, antitrust law, federal and state regulations, and complex markets. For the past several decades, courts and commentators have analyzed issues presented by brand-name and generic drug companies in the "small molecule" setting. But just as they have begun to comprehend the multiple moving parts, a new frontier has arisen involving large molecules known as "biologics."

Biologics differ from small-molecule drugs along multiple axes. They are more expensive, costing hundreds of millions of dollars to develop. They cannot be precisely replicated, followed by "biosimilars" rather than generics. They are governed not by the Hatch-Waxman Act[1] but by the Biologics Price Competition and Innovation Act ("BPCIA").[2] And they present a blank slate on which issues of innovation and competition will be hammered out in the decades to come. Given that biologics promise revolutionary advances like treatments for previously incurable diseases and cancer regimens offering substantial benefits over chemotherapy, the stakes could not be higher.

The small-molecule setting has been replete with collusive behavior such as "reverse payment" agreements by which brands and generics settle patent litigation and unilateral conduct by which brands modify their products to block generics, file frivolous government petitions, manipulate the regulatory regime, and deny materials generics need to enter the market. In contrast, the U.S. Food and Drug Administration ("FDA") has, to date, approved only seven biosimilars, with courts and policy-makers yet to address the significant antitrust concerns implicated by competition between biologics and biosimilars. How likely are the forms of conduct that have arisen in the small-molecule setting to appear in the biologics industry? And if these behaviors occur, how should antitrust law respond? This Article addresses these questions, offering an antitrust framework to analyze the conduct most likely to arise.

1. Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355 (2012).

2. Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119, 804 (2010) (codified as amended in scattered sections of the U.S. Code) (BPCIA was enacted under Title VII of PPACA).

Part II provides a primer on biologics, offering a brief history before focusing on the relevant science and markets. Part III then introduces the federal and state regulations addressing small-molecule drugs and biologics. Part IV, the heart of the Article, offers a tour of seven forms of conduct that antitrust law has addressed in the small-molecule setting and that could arise with biologics: reverse-payment settlements, "product hopping," regulatory abuse, denials of samples, "citizen petitions," disparagement, and price collusion. For each of these, it predicts the likelihood of the behavior and provides an antitrust assessment.

Part IV also predicts that certain conduct will be more likely in the biologic setting. Most notably, because of the importance of marketing and the difference with follow-on products, we believe biologic manufacturers will more frequently disparage biosimilars. We also predict that increased complexity will result in more citizen petitions. And we anticipate that the private nature of patent litigation and notice will lead to more collusion and (at least in the short term) regulatory abuse. In fact, we even foresee the use of *submarine patents*, universally acknowledged to be buried by 1990s patent law changes, and an emergence of *shell licensing* that has garnered criticism in the setting of "patent trolls." At the same time, biologics' complexity will tend to reduce the incidence of product hopping, and the smaller losses from generic entry and increased use of *inter partes* review ("IPR")[3] should reduce the number of reverse-payment settlements. Finally, Part IV encourages robust antitrust analysis of these forms of conduct similar to what courts have applied in the small-molecule setting. But because increased complexity reduces the likelihood of sham citizen petitions, we suggest a modestly more deferential antitrust analysis.

Antitrust finds itself at a unique and crucial moment: poised at the precipice of a new industry but able to draw on decades of case law in an analogous setting that has addressed issues of competition and innovation. It is far from obvious how much courts can—or should—take from that setting. This Article assists in this task by determining which antitrust principles and doctrines should be exported to the setting of biologics while appreciating the differences that counsel against such extrapolation. Given the importance of life-saving cancer treatments and an impending $400 billion market, there is no time to waste.

II. BIOLOGICS

A central challenge facing any analysis of biologics and biosimilars stems from the significant difference between this relationship and that of brands and generics. After providing a brief history of biologics, Part II explores the scientific differences between small molecules and biologics, including their volatility and follow-on manufacturers' inability to replicate the original medicine. It also analyzes market distinctions that result in differences in the pricing and marketing of the drugs.

3. 35 U.S.C. § 311 (2012).

A. History

In a nutshell, the pharmaceutical industry consists of small-molecule drugs and biologics.[4] For most of the twentieth century, innovation resulted in small-molecule therapies in the form of compounds produced through chemical synthesis.[5] From proton-pump inhibitors to treat heartburn (Prilosec[6] and Nexium[7]) to blood thinners (Plavix[8]), each drug represented the end result of discovery in the field of chemistry.[9] From the 1940s through the mid-1970s, high fixed costs and development risks resulted in few successful entrants.[10] Firms with vast chemical libraries, like Merck, had a significant advantage in identifying new treatments through random screenings against the libraries.[11] Competition stagnated.

All of this changed in 1976 when Genentech emerged as a pioneer in specialized biotechnology.[12] The company's founders developed a new technique for genetically engineering DNA in living cells, known as recombinant DNA.[13] This critical advance formed the core of the biologics revolution.[14] A *biologic* is a large, complex molecule derived from a living organism, most commonly a protein.[15] Through an intricate manufacturing process, biologics are harvested in genetically modified cell lines[16] and purified through complex, lengthy procedures.[17]

In the past 30 years, a number of valuable biologics have entered the market.[18] The FDA has explained that the field "represent[s] the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions" that have "no other treatments

4. LAURENCE A. BORDEN, PHARMACEUTICAL AND BIOTECH PATENT LAW § C:1 (2017).

5. GARY P. PISANO, SCIENCE BUSINESS: THE PROMISE, THE REALITY, AND THE FUTURE OF BIOTECH 26 (2006).

6. *Prilosec*, DRUGS.COM, https://www.drugs.com/prilosec.html (last updated Feb. 2, 2015).

7. *Nexium*, DRUGS.COM, https://www.drugs.com/nexium.html (last updated Jan. 20, 2015).

8. *Plavix*, DRUGS.COM, https://www.drugs.com/plavix.html (last updated Aug. 15, 2016).

9. JIE JACK LI, BLOCKBUSTER DRUGS: THE RISE AND DECLINE OF THE PHARMACEUTICAL INDUSTRY 44, 60–61, 119 (2014).

10. PISANO, *supra* note 5, at 81–82.

11. *Id.* at 82, 103.

12. *Id. See generally* SALLY SMITH HUGHES, GENENTECH: THE BEGINNINGS OF BIOTECH (2011).

13. HUGHES, *supra* note 12, at 19–20.

14. *See Biological Therapy for Cancer*, MAYO CLINIC (Dec. 5, 2014), http://www.mayoclinic.org/tests-procedures/biological-therapy-for-cancer/basics/definition/prc-20022365.

15. *What Are "Biologics?" Questions and Answers*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm (last updated Aug. 5, 2015) [hereinafter *What Are "Biologics?"*].

16. *See* Li Feng et al., *Cell Culture Processes for Monoclonal Antibody Production*, MABS, Sept.–Oct. 2010, at 466, 468–69, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958569/pdf/mabs0205_0466.pdf. Specialized cell lines are critical to developing monoclonal antibodies, which enlist the immune system to fight cancer. *Monoclonal Antibody Drugs for Cancer: How They Work*, MAYO CLINIC (Sept. 9, 2016) http://www.mayoclinic.org/diseases-conditions/cancer/in-depth/monoclonal-antibody/ART-20047808.

17. Jame Abraham, *Developing Oncology Biosimilars: An Essential Approach for the Future*, 40 SEMINARS ONCOLOGY S5, S10–S11 (2013).

18. *See* Lawrence K. Altman, *A New Insulin Given Approval for Use in U.S.*, N.Y. TIMES (Oct. 30, 1982), http://www.nytimes.com/1982/10/30/us/a-new-insulin-given-approval-for-use-in-us.html; Mantej Chhina, *Overview of Biological Products*, U.S. FOOD & DRUG ADMIN. (June 17, 2013), http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM356666.pdf.

available."[19] Procrit, for example, is an erythropoietin (kidney-produced hormone stimulating red blood cell formation[20]) used to treat anemia in, among others, HIV and cancer patients.[21] First approved in 1989, Procrit has the same biological effects as naturally occurring erythropoietin[22] and has been a commercial success, with annual revenues exceeding $1.1 billion.[23]

Monoclonal antibodies, the most frequently developed type of biologic,[24] include blockbuster products such as infection-reducing Neulasta,[25] as well as Humira[26] and Remicade,[27] both of which treat arthritis, colitis, and Crohn's disease.[28] In targeting unhealthy cells without harming healthy cells,[29] monoclonal antibodies have, when used with chemotherapy or radiation, dramatically increased survival rates. Just to pick one example, the development of Rituxan in the 1990s substantially improved the treatment of Non-Hodgkin's lymphoma, the most common form of blood cancer in adults.[30] Other types of biologics include vaccines, blood products, gene therapies, and cell therapies.[31] The importance of biologics stems from the science supporting the products.

B. Science

The science underlying biologics is profoundly different from that of small-molecule drugs. Small molecules are created through a series of chemical reactions known as chemical synthesis.[32] This process is relatively predictable, allowing generics to imitate brand drugs at low cost. Put another way,

19. *What Are "Biologics?"*, *supra* note 15.

20. Sjamak N. Nabil, *Erythropoietin* (*EPO, The EPO Test*), MEDICINENET.COM, http://www.medicinenet.com/erythropoietin/article.htm (last updated Jan. 15, 2016).

21. SARFARAZ K. NIAZI, BIOSIMILARS AND INTERCHANGEABLE BIOLOGICS: STRATEGIC ELEMENTS 560 (2016).

22. *Id.*

23. QUARTERLY RESULTS, FOURTH QUARTER 2016, SALES OF KEY PRODUCTS/FRANCHISES, JOHNSON & JOHNSON, http://files.shareholder.com/downloads/JNJ/5097946865x0x924677/ACE5F259-F6F1-4BB2-9D09-1075DD7F6E9C/Sales_of_Key_Products_Franchises_4Q2016.pdf (last visited Nov. 14, 2017).

24. One comprehensive report concluded that 338 of the 907 biologics in development were monoclonal antibodies. *See* PHRMA, MEDICINES IN DEVELOPMENT: BIOLOGICS 4–5 (2013), http://phrma.org/sites/default/files/pdf/biologicsoverview2013.pdf [hereinafter PHRMA REPORT].

25. NEULASTA, https://www.neulasta.com/ (last visited Aug. 31, 2017).

26. HUMIRA, https://www.humira.com/?cid=ppc_ppd_msft_franchise_brand_2015_humira_Exact_64X1790908 (last visited Nov. 12, 2017).

27. REMICADE, https://www.remicade.com/?utm_source=bing&utm_medium=cpc&utm_campaign=Branded&utm_content=RAIS%20-%20General&utm_term=remicade&gclid=CJnFzq2_hNICFSi2gQod1FgEaQ&gclsrc=ds (last visited Nov. 12, 2017).

28. *See generally* ROBERT BAZELL, HER-2: THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER (1998) (describing development of breast cancer treatment Herceptin and effect on women).

29. PHRMA REPORT, *supra* note 24, at 4.

30. Efrat Dotan et al., *Impact of Rituximab (Rituxan) on the Treatment of B-Cell Non-Hodgkin's Lymphoma*, PHARMACY & THERAPEUTICS, Mar. 2010, at 148, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2844047/#!po=23.6842; *see id.* (supplementing chemotherapy regimens with Rituxan improved patients' survival rate from 57% to 70%); *see also Model List of Essential Medicines*, WORLD HEALTH ORG. (19th ed. 2015), http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1 (listing Rituxan as essential medicine).

31. PHRMA REPORT, *supra* note 24, at 1, 4 ("Vaccines have historically been used as a preventative tool in infectious diseases, such as pneumonia, HIV and smallpox," but today are "used as therapies for cancer and other diseases.").

32. BORDEN, *supra* note 4, § C:5.1.

brands and generics can put the same pieces of a puzzle together in the same way to create the same image. Biologics, in contrast, blow up that paradigm, emphasizing not the individual pieces of the puzzle but the way the puzzle is constructed. Because "the product is the process"[33] and the use of living cells to create biologics is inherently sensitive,[34] there is higher variability and follow-ons cannot precisely replicate the original product.[35]

Challenges in biologic development stem from not only the complexity of the molecule but also from changes during the product's maturation.[36] Unlike the "single and mono-molecular entity" making up small molecules, the final form of biologics is "a complex mix of the same protein molecule under various structurally close [protein-varying] isoforms."[37] The complicated nature of biologic development is revealed by the uncertainties in the structure of a protein, a typical biologic.

A protein includes four structural levels: primary, secondary, tertiary, and quaternary.[38] The primary structure consists of the amino acid sequence, which is essential for biologic activity.[39] Even though drug developers can replicate an amino acid sequence,[40] individualized production and purification methods result in unpredictable structural folding at the secondary, tertiary, and quaternary levels (each of which addresses larger three-dimensional structures).[41] This unpredictability has dramatic effects, determining whether a drug confers therapeutic or toxic effects.[42] Adding to the complexity, even if a biosimilar manufacturer could replicate the structure of the biologic, *post-translational modifications* to the structure[43] could result in undetectable differences causing adverse patient reactions.[44]

33. JAMES T. O'REILLY & KATHARINE A. VAN TASSEL, FOOD AND DRUG ADMINISTRATION § 13:135 n.16 (Thomson Reuters, 4th ed. 2016).

34. *Id.*

35. In addition, biologics weigh significantly more than small molecules. A typical cancer-fighting monoclonal antibody biologic is 1,000 times heavier than a small-molecule aspirin. *Introducing Biologics & Biosimilars*, MERCK, https://www.merckclarifiesbiosimilars.com/biosimilars-market/what-are-biosimilars/what-is-a-biologic/ (last visited Sept. 4, 2017). As another example, Rituxan weighs 200 times more than the heavy small molecule Viagra. *Compare Rituxan Label*, FDA (2014), https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103705s5432lbl.pdf (143,859 grams/mole), *with Viagra Label*, FDA (Sept. 2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020895s045lbl.pdf (666 grams/mole).

36. NIAZI, *supra* note 21, at 16.

37. *Id.*

38. BORDEN, *supra* note 4, § C:5.2. Portions of this section are adapted from Carl J. Minniti III, Note, Sandoz v. Amgen*: Why Current Interpretation of the Biologic Price Competition and Innovation Act of 2009 is Flawed and Jeopardizes Future Competition*, 97 J. PAT. & TRADEMARK OFF. SOC'Y 172, 175 (2015).

39. Minniti, Sandoz v. Amgen, *supra* note 38.

40. *E.g.*, Ana Skrlin et al., *Comparison of the Physicochemical Properties of a Biosimilar Filgrastim with those of Reference Filgrastim*, 38 BIOLOGICALS 557 (2010).

41. Abraham, *supra* note 17, at S9.

42. *Id.*

43. Such modifications occur on a protein "catalyzed by enzymes after its translation by ribosomes is complete" and generally include the addition of a functional group to the protein. *Post-Translational Modifications*, NATURE.COM, http://www.nature.com/subjects/post-translational-modifications (last visited Nov. 14, 2017).

44. Abraham, *supra* note 17, at S10; *see* NIAZI, *supra* note 21.

Most therapeutic proteins induce a reflexive antibody response against the therapy introduced into the patient's body.[45] For that reason, immunogenicity—a triggered unwanted immune response[46]—plays a critical role in biologic development.[47] As a patient's body attempts to fight off foreign proteins, certain product-related factors elicit particular responses, including molecule design, impurities, and post-translational modifications.[48] The development of biologics is particularly difficult and unpredictable because the immunogenic response to proteins cannot be replicated in animal models to simulate an immune response in humans.[49]

If variability in biologic development and immunogenicity is a concern for the biologic manufacturer in making its *own* product, a *follow-on* maker will confront even higher hurdles. While these entities can rely on patent disclosures and other materials in the public domain, they will lack access to critical information the biologic manufacturer protects as a trade secret. Because biologics are "so closely defined by their manufacturing process," this secrecy blocks competition.[50] Finally, the effects of complexity and secrecy are exacerbated by the difficulty of even *analyzing* a protein's structure. The ability to use analytic techniques to demonstrate clinical comparability is more limited than for small-molecule drugs, with a biosimilar manufacturer not able to show that its product is identical to the biologic product.[51]

Unlike generic versions of small-molecule drugs, which are chemically identical to brand versions, the structural variability and complexity inherent in biologic development cause follow-on versions to strive for, at most, similarity.[52] These differences have direct effects on the relevant markets.

C. Markets

Biologics' complexity is accompanied by their timeliness, with a follow-on biosimilars market poised to explode. This development is even more crucial given that many blockbuster small-molecule drugs are in the midst of losing patent protection, with nearly $200 billion in brand sales subject to generic competition by 2025.[53] The end of a "golden age"[54] for small-molecule block-

45. Zuben E. Sauna, *Immunogenicity of Protein-based Therapeutics*, FDA (Feb. 29, 2016), https://www.fda.gov/biologicsbloodvaccines/scienceresearch/biologicsresearchareas/ucm246804.htm.

46. *Id.*

47. NIAZI, *supra* note 21, at 22.

48. *Id.*

49. *Id.* at 23 (urging regulatory agencies "to classify [certain biologics] into low and high immunogenicity potential and then provide guidance that is responsive to the inherent risk in their development and clinical use").

50. W. Nicholson Price II, *Regulating Secrecy*, 91 WASH. L. REV. 1769, 1794 (2016).

51. *See* Steven A. Berkowitz et al., *Analytical Tools for Characterizing Biopharmaceuticals and the Implications for Biosimilars*, NATURE REV. DRUG DISCOV, June 2012, at 527 (July 2012), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3714370/pdf/nihms487580.pdf.

52. *See* JUDITH A. JOHNSON, CONG. RES. SERV., R44620, BIOLOGICS AND BIOSIMILARS: BACKGROUND AND KEY ISSUES 1 (2016).

53. Van Eck, *Why the Patent Cliff is a Key Driver of Generic Drug Growth*, MARKET REALIST (Mar. 3, 2016, 1:58 PM), http://marketrealist.com/2016/03/patent-cliff-driver-generic-drugs-growth/.

54. LI, *supra* note 9, at 172–73.

busters has resulted in drug companies developing biologics,[55] planning to receive as much as 50% of their revenues from the medications in the near future.[56] Such a development will be profitable, with an average daily cost of $45 for a biologic vastly exceeding that of a $2 daily cost for a small-molecule drug.[57]

The biologic market, worth $46 billion in 2002, is expected to increase to $390 billion worldwide by 2020.[58] The top-selling U.S. drug of 2015, immune-system-treating biologic Humira, amassed more than $8 billion in sales.[59] Other top-selling biologics include arthritis-treating Enbrel (nearly $6 billion) and arthritis-, Crohn's disease-, and colitis-treating Remicade (more than $4 billion).[60] The rise of biologics could be met with an onslaught of biosimilars, with biologics worth $67 billion in global sales witnessing the expiration of patents by 2020.[61] But despite the clear market opportunity, biosimilar introduction has been relatively slow. One fundamental reason is that, unlike generics requiring expenditures of roughly $2 million, biosimilar development, involving more intensive and uncertain research and development, costs as much as $200 million.[62]

Congress enacted the Biologics Price Competition and Innovation Act of 2009 ("BPCIA")[63] in 2010, but it took until 2015 for the FDA to approve the first biosimilar: Zarxio, Sandoz's follow-on version of Amgen's billion-dollar neutropenia (anti-infection) therapy, Neupogen.[64] As of the date of this Article, the FDA has approved only seven biosimilars. In addition to Zarxio, Mvasi[65] received approval as a biosimilar to the $6.75 billion cancer therapy Avastin,[66] and five biosimilars are follow-on versions of three blockbuster inflammatory disease treatments, each in the top ten drugs sold in the United States: (1) Am-

55. *Id.* at 172.

56. *Id.*

57. Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Economics of Biosimilars*, AM. HEALTH DRUG BENEFITS, Sept. 2013, at 469 (2013).

58. *See* IMS INSTITUTE HEALTHCARE INFORMATICS, DELIVERING ON THE POTENTIAL OF BIOSIMILAR MEDICINES: THE ROLE OF FUNCTIONING COMPETITIVE MARKETS, (Mar. 2016), http://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf.

59. Troy Brown, *100 Best-Selling, Most Prescribed Branded Drugs Through March*, MEDSCAPE (May 6, 2015), http://www.medscape.com/viewarticle/844317#vp_1.

60. *US$67 Billion Worth of Biosimilar Patents Expiring Before 2020*, GENERICS & BIOSIMILARS INITIATIVE ONLINE (Jan. 20, 2014), http://www.gabionline.net/Biosimilars/General/US-67-billion-worth-of-biosimilar-patents-expiring-before-2020; *Merck, Samsung Bioepis Launch Discounted U.S. Remicade Alternative*, REUTERS (July 24, 2017, 7:07 AM) [hereinafter GENERICS & BIOSIMILARS INITIATIVE ONLINE], https://www.reuters.com/article/us-samsung-bioepis-johnson-johnson-remic/merck-samsung-bioepis-launch-discounted-u-s-remicade-alternative-idUSKBN1A91GL.

61. GENERICS & BIOSIMILARS INITIATIVE ONLINE, *supra* note 60.

62. Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 443 (2007).

63. Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119, 804 (2010) (codified as amended in scattered sections of the U.S. Code) (BPCIA was enacted under Title VII of PPACA).

64. Press Release, Fed. Trade Comm'n, FDA Approves First Biosimilar Product Zarxio (Mar. 6, 2015), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm.

65. Press Release, Fed. Trade Comm'n, FDA Approves First Biosimilar for the Treatment of Cancer (Sept. 14, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm576112.htm.

66. Alex Philippidis, *The Top 15 Best-Selling Drugs of 2016*, GEN. (Mar. 6, 2017), https://www.genengnews.com/the-lists/the-top-15-best-selling-drugs-of-2016/77900868.

jevita[67] and Cyltezo,[68] biosimilars to the $8.3 billion Humira; (2) Erelzi,[69] a biosimilar to the $5.9 billion Enbrel; and (3) Inflectra[70] and Renflexis,[71] biosimilars to the $4.6 billion Remicade.[72] Early indications point to biosimilars lowering costs. For example, both Zarxio[73] and Inflectra[74] are sold at a 15% discount from the biologic price.[75] And according to Renflexis sponsor Merck, the biosimilar product "will be introduced in the U.S. at a list price (wholesaler acquisition cost) of $753.39, representing a 35% discount off the current list price of Remicade."[76]

In the small-molecule setting, the entry of a single generic modestly lowers price.[77] As the previous paragraph showed, early returns from the biosimilars market are analogous. But while the entry of multiple small-molecule generics results in significant price erosion (50% with 2 generics and 75% with at least 6),[78] we predict that the reductions may be more modest given attempts to recoup biosimilar development costs, which greatly exceed those incurred by generics.[79] The market effects of biologics and biosimilars also will be shaped by the relevant laws and regulations.

67. Press Release, Fed. Trade Comm'n, FDA Approves Amjevita, a Biosimilar to Humira (Sept. 23, 2016), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm.

68. *Boehringer Ingelheim Pharmaceuticals, Inc. Receives FDA Approval for Cyltezo™ (adalimumab-adbm), a Biosimilar to Humira®, for the Treatment of Multiple Chronic Inflammatory Diseases*, PR NEWSWIRE (Aug. 29, 2017), http://www.prnewswire.com/news-releases/boehringer-ingelheim-pharmaceuticals-inc-receives-fda-approval-for-cyltezo-adalimumab-adbm-a-biosimilar-to-humira-for-the-treatment-of-multiple-chronic-inflammatory-diseases-300510787.html.

69. Press Release, Fed. Trade Comm'n, FDA Approves Erelzi, a Biosimilar to Enbrel (Aug. 30, 2016), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518639.htm.

70. Press Release, Fed. Trade Comm'n, FDA Approves Inflectra, a Biosimilar to Remicade (Apr. 5, 2016), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm.

71. Jonathan Cheng & Jonathan D. Rockoff, *FDA OKs Samsung Bioepis's Biosimilar Version Of J&J's Remicade*, WALL ST. J. (Apr. 21, 2017, 5:03 PM), https://www.wsj.com/articles/fda-oks-samsung-bioepiss-biosimilar-version-of-j-js-remicade-1492808596.

72. Brown, *supra* note 59 (all figures based on 2015 sales).

73. Ben Hirschler & Michael Shields, *Novartis Launches First U.S. "Biosimilar" Drug at 15 Percent Discount*, REUTERS (Sept. 3, 2015), http://www.reuters.com/article/us-novartis-drug-idUSKCN0R30C22 0150903.

74. Richard Harris, *Small Savings for Drugs Made to Mimic Biotech Blockbusters*, NPR (Oct. 19, 2016, 3:48 PM), http://www.npr.org/sections/health-shots/2016/10/19/498559386/small-savings-for-drugs-made-to-mimic-biotech-blockbusters.

75. *Id.*; *see also* Jonathan D. Rockoff, *Knockoffs of Biotech Drugs Bring Paltry Savings*, WALL ST. J. (May 5, 2016, 10:23 AM), http://www.wsj.com/articles/knockoffs-of-biotech-drugs-bring-paltry-savings-1462458209; Nancy Walsh, *Medicare to Cover Infliximab Biosimilar*, MEDPAGE TODAY (Jan. 6, 2017), http://www.medpagetoday.com/rheumatology/generalrheumatology/62393.

76. Press Release, Merck, Merck Announces U.S. Launch of RENFLEXIS™ (infliximab-abda), a Biosimilar of Remicade, for All Eligible Indications (July 24, 2017), http://investors.merck.com/news/press-release-details/2017/Merck-Announces-US-Launch-of-RENFLEXIS-infliximab-abda-a-Biosimilar-of-Remicade-for-All-Eligible-Indications/default.aspx.

77. FDA, GENERIC COMPETITION & DRUG PRICES (MAY 13, 2015), http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm.

78. *See* CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY ix (1998) [hereinafter CBO STUDY].

79. Grabowski et al., *supra* note 62, at 440 ("[Biosimilars] will have higher fixed costs from clinical testing and from manufacturing, [which will result in] less entry than would be expected for generic[s]," and because of the lack of competitors, biosimilars "will be relatively close in price to branded biologics.").

III. REGULATION

The regulatory regime plays a uniquely critical role in the pharmaceutical industry. The federal Hatch-Waxman Act and state substitution laws govern small-molecule brands and generics, while the BPCIA controls biologics and biosimilars. This Part introduces these regimes, highlighting their crucial roles in fostering competition and innovation.[80]

A. Hatch-Waxman Act

In 1984, Congress enacted the Hatch-Waxman Act.[81] In doing so, the legislature sought to increase generic competition and foster innovation in the pharmaceutical industry.[82]

First, Congress sought to promote generic competition. Generic drugs have the same active ingredients, dosage, administration, performance, and safety as patented brand drugs.[83] Despite the equivalence, generic firms were required, at the time of the Act, to engage in lengthy and expensive trials to demonstrate safety and effectiveness. The FDA approval process took several years, and because the required tests constituted infringement, generics could not begin the process during the patent term.[84] They therefore waited until the end of the term to begin these activities, which prevented them from entering the market until two or three years after the patent's expiration. At the time of the Hatch-Waxman Act, there was no generic equivalent for roughly 150 drugs whose patent terms had lapsed.[85]

The drafters of the Act lamented the "practical extension" of the patentee's "monopoly position" beyond expiration.[86] Relatedly, they sought to ensure the provision of "low-cost, generic drugs for millions of Americans."[87] Generic competition would "do more to contain the cost of elderly care than perhaps anything else this Congress has passed."[88]

One of the tools used to accelerate generic entry was an experimental use defense allowing generics to experiment on a brand drug during the patent

80. *See generally* Erika Lietzan, *Biosimilar Law and Regulation: An Essential Guide*, FOOD & DRUG L. INST., Monograph Series, June 2011, at 1, 1–60, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2220857 (providing an in-depth review of drug approval statutes from 1902 through 2010).

81. Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355 (2012).

82. This Section is adapted from Michael A. Carrier, *Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality*, 108 MICH. L. REV. 37, 41–51 (2009) [hereinafter Carrier, *Unsettling Drug Patent Settlements*].

83. *Generic Drugs: Questions and Answers*, FDA, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm (last visited Nov. 14, 2017). A generic sometimes can differ in modest ways from the brand; *see* FDA, CTR. FOR DRUG EVALUATION AND RESEARCH, ANDA SUITABILITY PETITIONS, at 1 (2013), https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM365676.pdf (describing suitability petitions that allow generic submission differing from brand drug "with respect to (1) route of administration, (2) dosage form, (3) strength, or (4) when one active ingredient is substituted for one of the active ingredients in a listed combination drug product").

84. CBO STUDY, *supra* note 78, at 38.

85. H.R. REP. NO. 98-857, pt. 1, at 17 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2650.

86. H.R. REP. NO. 98-857, pt. 2, at 4 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2688.

87. 130 CONG. REC. 24427 (1984) (statement of Rep. Waxman).

88. *Id.*

term.[89] Congress also allowed generics to avoid the expensive and lengthy new drug process by filing an Abbreviated New Drug Application ("ANDA").[90] To do this, a generic must show that its drug possesses the same active ingredient, route of administration, bioequivalence (rate and extent of drug absorption), and other characteristics as the brand version.[91]

At the center of the notice-and-litigation scheme, Congress required brands to identify patents they believed would be infringed by the marketing of generic drugs.[92] When the FDA approves a new drug, it lists the patents in a publication known as the *Orange Book*.[93] Named for its orange cover (but now published in electronic form and accessible on the Internet), the publication contains a list of all the drugs approved for marketing in the United States.[94]

An ANDA applicant must provide one of four certifications for each patent listed in the Orange Book, with the "Paragraph IV" certification receiving the most attention since, in claiming that the patent "is invalid or will not be infringed," the generic attempts to enter during the patent term.[95] As an incentive to encourage such filings, the Act allows the first Paragraph IV filer to obtain 180 days of exclusivity, which—because it allows generics to charge prices only modestly less than brand prices[96]—is (as the Supreme Court recognized) a "valuable" period "worth several hundred million dollars."[97]

In addition to promoting generic competition, the Act fostered innovation. In the early 1980s, the industry faced an "innovation crisis," with the number of new chemical entities entering human testing falling 81% from the late 1950s until the late 1970s.[98] The legislature thus authorized extension of the patent term, with the extension currently amounting to half the time the drug is in clinical trials plus the period spent awaiting FDA approval after trials.[99] Congress also provided for periods of nonpatent market exclusivity. A company that offers a drug with a new active ingredient is entitled to four or five years of exclusivity,[100] and new clinical investigations essential to approval (including new dosage forms, new uses, and adoption of over-the-counter

89. 35 U.S.C. § 271(e)(1) (2012).

90. FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY, at 5 (2002), https://www.ftc.gov/sites/default/files/documents/reports/generic-drug-entry-prior-patent-expiration-ftc-study/genericdrugstudy_0.pdf [hereinafter FTC, GENERIC DRUG STUDY].

91. *Id.*

92. JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 15 (2d ed. 2005).

93. FDA, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (last visited Nov. 14, 2017).

94. THOMAS, *supra* note 92, at 15.

95. 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2012); *see id.* § 355(j)(2)(A)(vii)(I–III) (the other three certifications apply where no patent information appears in the Orange Book, the patent has expired, and the generic will not seek approval until the patent expires).

96. FTC v. Actavis, Inc., 133 S. Ct. 2223, 2235 (2013).

97. *Id.*; *cf.* 35 U.S.C. §§ 271(e)(2)(A), (e)(4) (2012).

98. Maureen S. May et al., *New Drug Development During and After a Period of Regulatory Change: Clinical Research Activity of Major United States Pharmaceutical Firms, 1958 to 1979*, 33 CLINICAL PHARMACOLOGY THERAPEUTICS 691, 691 (1983).

99. 35 U.S.C. §§ 156(c), (g)(6) (extension can last up to 5 years and, together with remaining patent term, give patentee up to 14 years of protection).

100. 21 U.S.C. § 355(j)(5)(F)(ii). The exclusivity period is 4 years for generic filers certifying patent invalidity or noninfringement and 5 years for other generic filers (extendable to 7.5 years if litigation is filed in the fifth year after NDA approval). *Id.*

status)[101] receive three years of exclusivity.[102] Finally, Congress granted to patent holders that sue within 45 days of receiving a Paragraph IV notice an automatic 30-month stay of FDA approval.[103]

The Act's drafters emphasized the carefully balanced equilibrium between competition and innovation. Representative Henry Waxman underscored the "fundamental balance of the bill,"[104] and the Energy and Commerce Committee Report explained that allowing early generic challenges "fairly balanced" the exclusionary rights of patent owners with the "rights of third parties" to contest validity and market products not covered by the patent.[105]

On the whole, the Hatch-Waxman Act has been successful. In the decade after enactment, brands benefited from an increase in effective patent life from 7 to 12 years.[106] At the same time, generic drugs, which made up 19% of prescriptions in 1984,[107] increased to 88% in 2015.[108] By 2015, the average generic cost $8, less than one-fifth the brand's $44 price.[109] Despite these successes, many have voiced concern with regulatory evasion, in particular from settlements in which brands pay generics to delay entering the market. In the years since the passage of the Act, the drafters have expressed their disapproval of this regulatory evasion, with Senator Hatch finding such agreements "appalling"[110] and Representative Waxman explaining that the settlements were an "unfortunate, unintended consequence" of the Act that "turned the . . . legislation on [its] head."[111]

Regulatory evasion threatens not only the federal Hatch-Waxman Act but also state drug product selection ("DPS") laws. These laws, in effect in all fifty states today, allow—and in many cases require—pharmacists to substitute generic versions for brand prescriptions.[112] The laws are designed to address the disconnect in the industry between prescribing doctors, who are not directly responsive to drug pricing, and paying insurers and consumers, who do not directly select the prescribed drug.[113] In particular, DPS laws carve out a role for

101. 35 U.S.C. §§ 156(c), (g)(6).

102. 21 U.S.C. § 355(c)(3)(E)(iii).

103. *Id.* § 355(j)(5)(B)(iii).

104. 130 CONG. REC. 24425 (1984) (statement of Rep. Waxman).

105. H.R. REP. NO. 98-857, pt. 1, at 28 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2661.

106. *See generally* Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, INT'L J. TECH. MGMT., Nov. 2000, at 98, https://fds.duke.edu/db/attachment/182.

107. Ann M. Thayer, *30 Years of Generics*, 92 CHEMICAL & ENGINEERING NEWS (Sep. 29, 2014), http://cen.acs.org/articles/92/i39/30-Years-Generics.html.

108. GENERIC PHARMACEUTICAL ASS'N, GENERIC DRUG SAVINGS IN THE U.S. 1 (7th ed. 2015) [hereinafter GPhA, GENERIC DRUG SAVINGS], http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf.

109. *Medicines Use and Spending in the U.S.–A Review of 2015 and Outlook to 2020*, IMS HEALTH (Apr. 2016), http://www.imshealth.com/en/thought-leadership/quintilesims-institute/reports/medicines-use-and-spending-in-the-us-a-review-of-2015-and-outlook-to-2020.

110. 148 CONG. REC. S7566 (daily ed. July 30, 2002) (statement of Sen. Hatch).

111. Motion and Brief for Representative Henry A. Waxman as Amicus Curiae Supporting Petitioner at *v, FTC v. Schering-Plough Corp., 548 U.S. 919 (2006) (No. 05-273).

112. Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1017 (2010) [hereinafter Carrier, *A Real-World Analysis*].

113. BUREAU OF CONSUMER PROTECTION, DRUG PRODUCT SELECTION: STAFF REPORT TO THE FTC 2–3 (1979) [hereinafter DRUG PRODUCT SELECTION REPORT].

pharmacists, who are more sensitive than doctors to prices.[114] The laws typically allow pharmacists to substitute a generic version if it is therapeutically equivalent to the brand, which means that it is bioequivalent[115] and has the same active ingredient, form, dosage, strength, and safety and efficacy profile.[116]

B. BPCIA

As comprehensive as it is, the Hatch-Waxman Act does not apply to biologics or biosimilars. To address the expiration of patents claiming first-generation biologics and promote competition for such highly priced drugs, Congress passed the BPCIA.[117] Ultimately enacted as part of the Patient Protection and Affordable Care Act in 2010,[118] the law was the culmination of nearly a decade of discussion, lobbying, and negotiation.[119] The BPCIA is a complex and multifaceted statute. As the Federal Circuit opined in only its second biosimilars case: "Winston Churchill once described Russia as a riddle wrapped in a mystery inside an enigma . . . [t]hat is this statute."[120] The following three subsections explain how the BPCIA regulates (1) biologic approval, (2) biosimilar approval, and (3) the carefully choreographed scheme for resolving patent disputes.

1. Biologic Approval

New biologic drug products are approved under the BPCIA.[121] Known as a *Biologic License Application* ("BLA"), a manufacturer cannot introduce its biologic product into interstate commerce without FDA approval.[122] The statute defines a *biologic product* as:

> [A] virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[123]

114. ALISON MASSON & ROBERT L. STEINER, GENERIC SUBSTITUTION AND PRESCRIPTION DRUG PRICES: ECONOMIC EFFECTS OF STATE DRUG PRODUCT SELECTION LAWS 7 (1985).

115. FDA, *Orange Book*, *supra* note 93.

116. *Id.*

117. Patient Protection and Affordable Care Act, Pub. L. No. 111–148, §§ 7001–03, 124 Stat. 804 (2010). The statute is codified in Section 351 of the Public Health Services Act ("PHSA"), Pub. L. No. 105–115, § 123, 111 Stat. 2296, 2323 (1997). Biologics were originally governed by the Biologics Act of 1902. Pub. L. No. 57–244, 32 Stat. 728 (1902). Congress recodified this scheme as Section 351 of the PHSA in 1944, Pub. L. No. 78–410, 58 Stat. 682, 702–03 (1944), and streamlined it in 1997. For a history of FDA regulation of biological products, see Lietzan, *supra* note 80.

118. Pub. L. No. 111–148, 124 Stat. 119 (2010).

119. *See generally* Krista Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010).

120. Amgen v. Sandoz, 794 F.3d 1347, 1351 n.1 (Fed. Cir. 2015).

121. 42 U.S.C. § 262 (2012).

122. *Id.* § 262(a).

123. *Id.* § 262(i)(A).

In addition to demonstrating that its product is "safe, pure, and potent," a BLA sponsor also must demonstrate that its manufacturing facility satisfies required standards.[124]

An approved biologic receives two concurrently running exclusivity periods, each of which begins when its BLA is approved.[125] In the shorter exclusivity period, the FDA will not *accept* an application from a biosimilar manufacturer for 4 years after the reference product's approval.[126] In the longer exclusivity period, beginning after 4 years have passed, the FDA is able to accept biosimilar applications but is not able to *grant approval* for 8 years.[127] During this period, the biosimilar applicant can proceed through the FDA approval process and patent-litigation scheme described below.[128]

2. Biosimilar Approval

The BPCIA provides an abbreviated approval pathway for follow-on competition.[129] To gain approval as a biosimilar under the BPCIA, an applicant must show that:

> [T]he biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and . . . there are no clinically meaningful differences between the biological product and the reference product in term of safety, purity, and potency of the product.[130]

Whether a follow-on biologic is *highly similar to* and has *no clinically meaningful differences from* the referenced product is a product-specific inquiry that likely will require dialogue with the FDA throughout the biosimilar development process.[131] A biosimilar maker will need to introduce data disclosing manufacturing processes and facility standards and compare its product with the reference product, with the FDA making its decision based on the totality of the evidence.[132]

The benefits of obtaining follow-on approval under the BPCIA differ from those under the Hatch-Waxman scheme. Unlike the small-molecule setting, in which the first generic to file a Paragraph IV challenge is eligible for a 180-day period of exclusivity, the first-to-file biosimilar does not benefit from such protection.[133] Rather, exclusivity is granted only to the first biosimilar found to be *interchangeable*.[134] To attain this status, the applicant must show

124. *Id.* § 262(a)(2)(C).
125. *Id.* § 262(k)(7).
126. *Id.* § 262(k)(7)(B).
127. *Id.* § 262(k)(7)(A).
128. *See infra* Subsection II.B.3.
129. 42 U.S.C. § 262(k).
130. *Id.* § 262(i)(2).
131. FDA, SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY, at 4 (2015), http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM291128.pdf.
132. *Id.* at 7; 42 U.S.C. § 262(k)(2)(A)(i)(V).
133. 42 U.S.C. § 262(k)(6). The legislative history indicates that a 2009 FTC report (which contended that an exclusivity period was "unnecessary to encourage the development and marketing" of biosimilars) convinced Congress not to grant exclusivity. *See* Carver et al., *supra* note 119, at 788–89.
134. 42 U.S.C. § 262(k)(2)(A)(i) .

that the follow-on version (1) is biosimilar to the reference product and (2) can be expected to produce the same clinical result as the reference product in any given patient.[135] For products administered more than once to an individual, the follow-on maker must show that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[136] If the applicant seeking interchangeability can meet this standard, it will receive exclusivity, which expires (if certain other litigation thresholds are not reached earlier) one year after commercial marketing.[137]

Just like states have allowed (or required) generic drugs to be substituted for brands,[138] some states allow substitutability for interchangeable biologics.[139] As of the date of this Article, no biosimilar has received interchangeability status. That is not a surprise given that such a showing (1) will tend to be more expensive than developing biosimilars (because of the need to show the same clinical result and, in many cases, undertaking clinical trials) and (2) may not offer significant market rewards since the FDA can continue to approve biosimilars during the exclusivity period.[140]

3. Patent Resolution

The lack of patent notice in the BPCIA provides another fundamental (and perhaps the most significant) distinction with the Hatch-Waxman Act. In the small-molecule setting, the FDA publishes the Orange Book, an annual list of approved drugs and associated patents,[141] and a new drug sponsor must list the patents it could reasonably assert against a proposed generic.[142] If the generic invalidates the patents or demonstrates noninfringement, it can immediately enter the market.[143] This structure offers a predictability for generics that is absent in the setting of biologics.

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135. *Id.* § 262(k)(4)(A)(i)–(ii). According to a 2017 draft guidance from the FDA, applicants must "produce the same clinical result as the reference product in all of the licensed conditions of use." FDA, Draft, DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT: GUIDANCE FOR INDUSTRY, at 3 (2017) [hereinafter FDA, DEMONSTRATING INTERCHANGEABILITY], http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf.

136. 42 U.S.C. § 262(k)(4)(B).

137. *Id.* § 262(k)(6) (exclusivity expires on earliest of (1) one year after commercial marketing, (2) 18 months after court judgment or dismissal in patent litigation, (3) 42 months after approval if litigation pending, and (4) 18 months after approval if applicant has not sued).

138. *See supra* notes 112–16 and accompanying text.

139. For a review of state substitution laws, see Richard Cauchi, *State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars*, NAT'L CONFERENCE STATE LEGISLATURES (Sept. 1, 2017), http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx.

140. Erika Lietzan, *The Uncharted Waters of Competition and Innovation in Biological Medicines*, 44 FLA. ST. L. REV. (forthcoming 2017). Another reason is that the FDA released an initial draft guidance on the data necessary to show interchangeability only in January 2017. *See* FDA, *Demonstrating Interchangeability*, *supra* note 135, at 3.

141. *See supra* note 93 and accompanying text.

142. 21 U.S.C. §§ 355(b)(1), (c)(2).

143. *Id.* § 355(j)(F)(ii).

The BPCIA does not require the FDA to maintain an Orange Book and does not compile a public listing of patents alleged to claim a biologic's subject matter.[144] Instead, the law establishes a complex framework to identify relevant patents to be litigated. The legislative history reveals that the purpose of the patent-exchange provisions was to "ensure that litigation surrounding relevant patents will be resolved expeditiously and prior to the launch of the biosimilar product, providing certainty to the applicant, the reference product manufacturer, and the public at large."[145] Given the important role manufacturing and product-specific development play in the biosimilar market, reliance on the parties to negotiate litigation of only a subset of patents sheds light on the purpose of the patent dance as industry actors compromise and narrow the range of patents at issue.[146]

Patent resolution occurs in two phases. In Phase One, the parties engage in what is widely known as the *patent dance*,[147] by which the product sponsor and biosimilar applicant identify the patents that will be litigated.[148] In contrast to the Hatch-Waxman Act, pursuant to which only certain types of patents can be listed in the Orange Book (thereby yielding a 30-month stay), the BPCIA allows the biologic to assert any patent against which it "believes a claim of patent infringement could be reasonably asserted."[149]

The BPCIA's patent dance is a 6-step process that is triggered 20 days after the FDA accepts the biosimilar's application and that lasts approximately 8 months.[150] First, the applicant provides the sponsor with a copy of its application and "other information" describing the manufacturing process.[151] Second, the sponsor, within 60 days, provides the applicant with a list of patents for which it believes a claim of patent infringement could reasonably be asserted.[152] Third, within 60 days, the applicant can submit its own patent list for which it believes a reasonable infringement claim could be asserted as well as a detailed statement (on a claim-by-claim basis) asserting invalidity, noninfringement, or unenforceability.[153] Fourth, the sponsor replies by offering its

144. In September 2014, the FDA published the first edition of the "Purple Book." FDA, *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm (last visited Nov. 14, 2017). Unlike the Orange Book, the Purple Book (which lists information such as product name and approval date) does not offer patent information. Because its contents do not play a role in litigation and cannot be used to delay follow-on entrants, the Purple Book does not threaten competition. *Id.*

145. *Biologics and Biosimilars: Balancing Incentives for Innovation: Hearing Before the Subcomm. on Courts and Competition Policy of the H. Jud. Comm.*, 111th Cong. 9 (July 14, 2009) (statement of Rep. Eshoo).

146. *See* Carver et al., *supra* note 119, at 816–18.

147. *E.g.*, Brief for the Biosimilars Council as Amicus Support for Petitioners, at 2, Apotex, Inc. v. Amgen, Inc., 2016 WL 6082331, No. 16-332 (Fed. Cir. filed Oct. 14, 2016).

148. 42 U.S.C. § 262(l)(2)–(6) (2012).

149. *Id.* § 262(l)(3)(A)(i); DAVID K. BARR, PHARMACEUTICAL AND BIOTECH PATENT LAW § 14:4.6[B] (2010) ("[A biologic manufacturer] can include . . . not only composition and method-of-use patents, but also method-of-making patents that it believes will be infringed by the manufacture of the biosimilar product.").

150. BARR, *supra* note 149, §14:4.6[D].

151. 42 U.S.C. § 262(l)(2)(A).

152. *Id.* § 262(l)(3)(A)(i).

153. *Id.* § 262(l)(3)(B).

own detailed statement responding to the applicant's positions on invalidity, noninfringement, and unenforceability.[154]

Once the parties submit their contentions, the fifth step of the patent dance calls for *good-faith negotiations* on the patents to be litigated.[155] If no agreement is reached, step six calls for the final patent list exchange.[156] The applicant provides the sponsor with the number of patents it will designate in its Phase One list.[157] Then, on an agreed date, the parties simultaneously exchange a final list of patents to be litigated.[158] The sponsor cannot list more patents than the number selected by the biosimilar applicant.[159]

After the parties have proceeded through the patent dance, the sponsor has 30 days to file suit against the applicant.[160] If the parties agreed on specific patents during the negotiations, those patents will be the subject of litigation.[161] If the parties did not reach such agreement, the sponsor could sue the applicant on all the patents included on both lists at step six.[162]

Phase Two, meanwhile, allows the biologic manufacturer to pursue, even years later, those patents included in the initial list but not litigated in Phase One.[163] If the biosimilar applicant provides the biologic with the information required in Phase One, then neither the biologic nor biosimilar applicant can bring a declaratory action on any other patent before the applicant provides advance notice of the first commercial marketing of the product.[164] Phase-Two litigation also includes newly issued or licensed patents obtained by the biologic during Phase One.[165]

In short, and in contrast to the Hatch-Waxman Act, the BPCIA's patent resolution provisions are centered on private negotiation between the parties.

IV. ANTITRUST ANALYSIS

In the past few decades, courts have applied antitrust scrutiny to a range of conduct in the pharmaceutical industry: reverse-payment settlements between brands and generics, product hopping from one version of a drug to another, regulatory abuse, citizen petitions filed with the FDA, the denial of samples, disparagement, and collusion.

154. *Id.* § 262(l)(3)(C).
155. *Id.* § 262(l)(4).
156. *Id.* § 262(l)(5).
157. *Id.* § 262(l)(5)(A).
158. *Id.* § 262(l)(5)(B).
159. *Id.* § 262(l)(5)(B)(ii)(I). If the biosimilar applicant does not select any patents, the sponsor may select one patent. *Id.* § 262(l)(5)(B)(ii)(II).
160. *Id.* § 262(l)(6)(A).
161. *Id.*
162. *Id.* § 262(l)(6)(B). If new patents are issued during or after the patent dance, the biologic must supplement its patent list within 30 days of obtaining the patents. *Id.* § 262(l)(7). The applicant must then respond to the biologic with its invalidity, noninfringement, or unenforceability arguments. *Id.*
163. *Id.* § 262(l)(8)(B)(i)–(ii).
164. This notice must occur no later than 180 days before such marketing. *Id.* § 262(l)(8)–(9); *see* Sandoz Inc. v. Amgen Inc., 137 S. Ct. 1664 (2017) (interpreting biosimilar framework to permit earlier follow-on marketing than the Federal Circuit had allowed by letting applicant provide notice either before or after receiving FDA approval).
165. 42 U.S.C. § 262(l)(7).

Given the emerging nature of the industry, there has been limited consideration of how antitrust law should apply to biologics.[166] This Part tackles this project. It highlights the different biologics context, with more complex products, fewer competitors, a nonidentical relationship between the original and follow-on product, less notice of patents that could be infringed, and a regulatory regime addressing patents through private information exchange rather than public listing.[167]

For each of the types of conduct mentioned in the previous paragraph, the Part analyzes the likelihood of such behavior in the biologics setting and proposes a framework for antitrust analysis. It concludes that disparagement, collusion, citizen petitions, and (at least in the short term) regulatory abuse are more likely to occur while product hopping and reverse-payment settlements are less likely. And it calls for antitrust scrutiny as robust as that in the small-molecule setting for each of these types of behavior with modestly less rigorous analysis of citizen petitions.[168]

A. Patent Settlements

For the past two decades, no antitrust issue in the pharmaceutical industry has received as much attention among courts and commentators as settlements. The typical arrangement that has been evaluated involves a brand paying a generic to settle patent litigation and delay entering the market. In this Section, we predict that the frequency of such reverse-payment[169] settlements involving biologics and biosimilars should be modestly less and that an analysis similar to that developed in the Hatch-Waxman context should apply.

166. The most comprehensive analysis comes from a 2009 FTC report issued before the enactment of the BPCIA. *See* FTC, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION: A FEDERAL TRADE COMMISSION REPORT (June 10, 2009), https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901 biologicsreport.pdf (analogizing competition between biologics and biosimilars to competition between brands in small-molecule setting and contending that existing incentive structure supported innovation and competition).

167. In the first antitrust lawsuit in the biologics industry, Pfizer recently sued Johnson & Johnson, challenging exclusive contracts, rebates, and bundling arrangements with insurance company payors and healthcare providers that protected (arthritis- and Crohn's-treating) Remicade from competition and foreclosed nearly the entire market for the biosimilar manufacturer's Inflectra. Complaint, Pfizer Inc. v. Johnson & Johnson, Case 2:17-cv-04180-JCJ (E.D. Pa. filed Sept. 20, 2017). Such allegations, which have more typically been raised outside the pharmaceutical setting, have also recently been alleged in the small-molecule setting. *See* Shire US v. Allergan, Case 2:17-cv-07716 (D.N.J. filed Oct. 2, 2017) (making similar allegations). Intermediaries play an important role in drug pricing and—given the web of private contracts and complex insurance regulatory systems—deserve scrutiny. *See* Michael A. Carrier & Carl J. Minniti III, *The Untold EpiPen Story: How Mylan Hiked Prices By Blocking Rivals*, 102 CORNELL L. REV. ONLINE 53, 58 n.38 (2016) (noting difficulty EpiPen competitor faced in gaining market share when removed from preferred drug list of top pharmacy benefit manager ("PBM")).

168. We do not address in detail trade secret issues, which (in not blocking independent discovery and being less likely to present market power) do not as directly threaten antitrust concerns. We note below, however, that biologic manufacturers' desire to protect their trade secrets could increase the number of settlements. *See infra* notes 207–09 and accompanying text.

169. The compensation is referred to as a "reverse payment" because of the direction in which the payment flows. Unlike typical patent settlements in other industries, in which an alleged infringer pays the patentee to enter the market, these settlements involve payments from the patentee to the alleged infringer to stay out of the market.

1. Hatch-Waxman Act

In its first enforcement related to settlements, the Federal Trade Commission ("FTC") entered into two consent decrees in 2000.[170] Appellate court review began in 2003 when the Sixth Circuit held that a settlement that restricted entry on the patent at issue as well as other patents was "a horizontal agreement to eliminate competition, . . . a classic example of a per se illegal restraint of trade."[171] Courts, however, quickly retreated from such scrutiny, adopting a test that essentially immunized activity falling within the *scope of the patent*. Between 2005 and 2012, the Eleventh Circuit,[172] Second Circuit,[173] and Federal Circuit[174] applied tests to determine whether "the agreements restrict[ed] competition beyond the exclusionary zone of the patent."[175] The trend favoring deference relied on not only the scope of the patent, but also the importance of settlements, the presumption of patent validity, and the "natural" status of reverse payments.[176]

The tide turned in July 2012, when the Third Circuit concluded that a reverse payment was "prima facie evidence of an unreasonable restraint of trade."[177] In 2013, in the landmark case of *FTC v. Actavis*,[178] the Supreme Court rejected the scope-of-the-patent test, concluding that it was "incongruous" to "determine antitrust legality by measuring the settlement's anticompetitive effects solely against patent law policy, rather than by measuring them against procompetitive antitrust policies as well."[179] The Court held that the settlement at issue had the "potential for genuine adverse effects on competition" since "payment in return for staying out of the market . . . keeps prices at patentee-set levels."[180] And the Court found that these settlements could occur because of the first-filing generic's 180-day exclusivity, which reduced the incentives for later-filing generics to challenge patents.[181] After *Actavis*, lower courts have continued to apply antitrust scrutiny, addressing issues such as the definition of payment,[182] form of antitrust analysis,[183] role of the patent merits,[184] and causation.[185]

170. Press Release, Fed. Trade Comm'n, FTC Charges Drug Manufacturers with Stifling Competition in Two Prescription Drug Markets (Mar. 16, 2000), https://www.ftc.gov/news-events/press-releases/2000/03/ftc-charges-drug-manufacturers-stifling-competition-two.

171. *In re* Cardizem CD Antitrust Litig., 332 F.3d 896, 908 (6th Cir. 2003).

172. FTC v. Watson Pharm. Inc., 677 F.3d 1298, 1312 (11th Cir. 2012); Schering-Plough Corp. v. FTC, 402 F.3d 1056, 1076 (11th Cir. 2005).

173. *In re* Tamoxifen Citrate Antitrust Litig., 466 F.3d 187, 208–09, 213 (2d Cir. 2006).

174. *In re* Ciprofloxacin Hydrochloride Antitrust Litig., 544 F.3d 1323, 1339 (Fed. Cir. 2008).

175. *Id.* at 1336.

176. Carrier, *Unsettling Drug Patent Settlements*, *supra* note 82, at 60–66.

177. *In re* K-Dur Antitrust Litig., 686 F.3d 197, 218 (3d Cir. 2012).

178. 133 S. Ct. 2223 (2013).

179. *Id.* at 2231.

180. *Id.* at 2234–35.

181. *Id.* at 2235.

182. *E.g.*, *In re* Loestrin 24 Fe Antitrust Litig., 814 F.3d 538, 549 (1st Cir. 2016); King Drug v. Smithkline Beecham, 791 F.3d 388, 394 (3d Cir. 2015).

183. *In re* Cipro Cases I & II, 348 P.3d 845, 860–63 (Cal. 2015); *In re* K-Dur Antitrust Litig., 2016 WL 755623, at *10 (D.N.J. Feb. 25, 2016).

184. Time Ins. v. AstraZeneca, 52 F. Supp. 3d 705, 712 (E.D. Pa. Oct. 1, 2014); FTC v. Cephalon, 36 F. Supp. 3d 527, 531 (E.D. Pa. 2014).

2. BPCIA

Although various factors point in different directions, we believe there will be fewer reverse-payment settlements between biologics and biosimilars. For the settlements that occur, however, we propose an antitrust framework similar to that developed in the Hatch-Waxman setting.

a. Likelihood

Because of the more modest effects of biosimilar entry, biologics' first-mover advantages, and increased use of IPR[186] proceedings, settlements involving payment and delayed entry[187] should be less likely in the biologic setting.

First, biologic manufacturers do not face losses as drastic from biosimilar entry as brands face from generic entry. When multiple generics enter the market, the price falls dramatically, giving the brand every incentive to delay entry as long as possible.[188] In contrast, given high development costs and a more finite universe of potential biosimilar entrants,[189] the price likely will not fall as significantly upon biosimilar entry, which may reduce biologics' urgency to enter into settlements.[190] Although there is no first-filer exclusivity period for biosimilars like there is in the Hatch-Waxman setting,[191] the universe of biosimilars that could enter the market should be smaller because of the significant cost and time it takes to develop a product. In contrast to the roughly 3 years it takes to develop a generic,[192] biosimilar production takes 8 to 10 years.[193] And unlike the roughly $2 million it typically costs to develop a generic drug,[194] a biosimilar product could cost $200 million.[195] In short, reduced competition will lead to more modest price reductions.[196]

Second, these more modest effects are compounded by biologic manufacturers' lasting first-mover advantage. Unlike in the case of small molecules, where automatic substitution brings about instant price erosion,[197] a biologic

185. *See In re* Nexium Antitrust Litig., 309 F.R.D. 107, 127 (D. Mass. 2015).

186. 35 U.S.C. § 311 (2012).

187. Delay is determined from the date of settlement. The Supreme Court's rejection of the scope-of-the-patent test eliminated the expiration of the patent as the point of comparison. FTC v. Actavis, 133 S. Ct. 2223, 2231 (2013).

188. *See supra* notes 77–78 and accompanying text.

189. *See infra* notes 192–95 and accompanying text.

190. *See supra* note 79 and accompanying text.

191. Interchangeable filers can obtain such exclusivity, but as of the date of this Article, there have been no such filers. For potential explanations, see *supra* note 140 and accompanying text.

192. Raymond Donninger et al., *Key Considerations in Biosimilars Development*, BIOPHARM. INT'L (Oct. 1, 2012), http://www.biopharminternational.com/key-considerations-biosimilars-development.

193. Dan Stanton, *Number of Biosimilar Developers Growing as Costs Plummet, Say CPhl Experts*, BIOPHARMA (Oct. 21, 2015), http://www.biopharma-reporter.com/Markets-Regulations/Number-of-biosimilar-developers-growing-as-costs-plummet-say-experts.

194. Blackstone & Fuhr, *supra* note 57.

195. *See supra* note 62.

196. *See supra* note 78 and accompanying text.

197. *See supra* Section II.B.

name's strength,[198] coupled with confidence in the original product, will play a more prominent role in forestalling competition. Providers may be "willing to pay a premium . . . to avoid the various issues and costs involved with dealing with patients and physicians concerning a switch to biosimilars."[199] Relatedly, the first biosimilar in a category faces a first-mover *disadvantage* in confronting barriers to entry such as prescriber and patient education, consumer reluctance, and more uncertain FDA approval.[200] These first-mover advantages and disadvantages do not appear in the small-molecule setting given the prevalence of state substitution laws and more direct overlap between brands and generics.

A third explanation stems from the role of IPR proceedings, which have allowed biosimilars to clear the field before the patent dance, thus decreasing the temptation to enter into settlements. A central feature of the 2011 America Invents Act,[201] IPRs offer any interested party the opportunity to challenge patent validity on grounds of novelty or obviousness.[202] Early trends have revealed biosimilars challenging biologic patents through IPR proceedings even before filing a biosimilar application.[203] While IPR tactics have increasingly been employed in the small-molecule setting, patent challenges to biologics at the Patent Office have been used more frequently, quickly becoming the norm.[204]

In addition, early trends in BPCIA litigation have revealed multiple biosimilar makers filing IPR petitions on the same patents.[205] And unlike generics

198. Just to offer one example, during each month between April 2016 and April 2017, with biosimilar competition looming, AbbVie's Humira was advertised on television more than any other product. Beth Snyder Bulik, *Lather, Rinse, Repeat for AbbVie, Lilly, Pfizer and Merck, April's Not-So-New Top Pharma TV Ad Spenders*, FIERCEPHARMA (May 17, 2017), http://www.fiercepharma.com/marketing/lather-rinse-repeat-for-abbvie-lilly-pfizer-and-merck-pharma-tv-ad-spending-april; Larry Dobrow, *MM&M 2014 Large Pharma Marketing Team of the Year: Humira*, MM&M (Jan. 1, 2014), http://www.mmm-online.com/features/mmm-2014-large-pharma-marketing-team-of-the-year-humira/article/326160/ (explaining that "[g]iven the patent expiration and more competition in the autoimmune space—[including biosimilars]—the Humira brand team seems to have its work cut out for it" and quoting Humira executive: "[t]he autoimmune market will continue to evolve and we anticipate Humira will remain a strong, sustainable growth brand").

199. LAZLO ENDRENYI ET AL., BIOSIMILAR DRUG PRODUCT DEVELOPMENT 425 (2017).

200. *Id.* at 426.

201. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

202. 35 U.S.C. § 311 (2012).

203. *E.g.*, Swiss Pharma. Int'l AG, Petitioner, v. Biogen Idec., Patent Owner, Case IPR 2016-00915 (Oct. 17, 2016) (denying institution of IPR proceedings brought by India's Swiss Pharma against formulation patent assigned to Biogen, which markets the $1.9 billion immunosuppressant Tysabri). By early 2017, 42 IPR petitions had been filed challenging biologic patents. *See* Big Molecule Watch, *Inter Partes Review: Pending IPRs*, https://www.bigmoleculewatch.com/iprs/ (last visited Nov. 13, 2017).

204. TIMOTHY J. SHEA, JR., 1 PATENT OFFICE LITIG. § 19.4 (Jason D. Eisenberg & Robert Greene Sterne eds., 2017) ("statistics show that post-grant proceedings are particularly favored by companies seeking to challenge key patents covering biopharmaceuticals on the market, and increasingly by biosimilar developers as they seek to obtain some measure of patent certainty well before the statutory litigation provided by the BPCIA even begins"); Zhiqiang Liu & Irena Royzman, *Biosimilar Makers Turn to IPRs Before Litigation Under the BPCIA*, BIOLOGICS BLOG (May 15, 2015), https://www.biologicsblog.com/biosimilar-makers-turn-to-iprs-before-litigation-under-bpcia/ ("A number of biosimilar makers have turned to [IPR] proceedings in order to litigate the validity of patents that cover their proposed products prior to submission of their biosimilar applications to FDA."); Christopher Noyes, *When Inter Partes Review Meets Hatch-Waxman Patents*, LAW360 (Sept. 9, 2014, 7:58 AM), https://www.law360.com/articles/572504/when-inter-partes-review-meets-hatch-waxman-patents (discussing role of IPR strategy in Hatch-Waxman cases).

205. *See, e.g.*, *Inter Partes Review: Pending IPRs*, *supra* note 203 (showing multiple biosimilars challenging Genentech's U.S. Patent No. 6,331,415).

that pursue business models of Paragraph IV filings followed by settlements, biosimilar makers may be less willing to settle because of their significant expenditures[206] and because they wish to satisfy shareholder expectations of launching lucrative biosimilars.[207] In short, settlements may be less likely in the biologics setting because of the use of IPR and biosimilars' need for launches.[208]

On the other hand, certain elements of the patent dance point in the direction of more settlements.[209] First, while the use of IPRs could reduce the number of biologic patents, a biologic with fewer of its patents surviving IPR proceedings could be more tempted to settle litigation in court. Second, when the patent-exchange provision commences, the biosimilar applicant must supply the sponsor with a copy of the application, as well as "such other information that describe[s] the . . . processes used to manufacture the biological prod-

206. *See* Grabowski et al., *supra* note 62, at 443 and accompanying text.

207. *E.g.*, *A Letter from Amgen's Chairman and Chief Executive Officer*, AMGEN, http://www.amgen.com/media/featured-news/2013/04/a-letter-from-amgens-chairman-and-chief-executive-officer/ (last visited Nov. 13, 2017) (top official tells shareholders that "[i]n early 2013, we announced plans to develop and manufacture six biosimilar molecules: four in the oncology disease area and two in inflammation" and that "[w]ith expectations to launch our first biosimilar product in 2017, we will be entering a rapidly growing segment of the biologics market").

208. An issue lying outside the scope of this Article worth attention in the coming years involves the antitrust implications of agreements with payments settling IPR challenges. As some have observed, "[o]nce the USPTO institutes a post-issuance proceeding, an ANDA applicant is in a powerful bargaining position to force an early settlement." SHEA, *supra* note 204, at § 21:20. The reason is that if the generic were to maintain its challenge after institution (*i.e.*, the critical, initial step a petitioner must meet to continue an IPR challenge), it will have already demonstrated a reasonable likelihood of showing that the challenged claims are unpatentable. *Id.* § 3:33 (citing 35 U.S.C. § 314(a) (2012)). For that reason, the generic can use this leverage of potential patent invalidation as a means to obtain a settlement. The possibility of anticompetitive harm may be ameliorated to some extent by the public's ability (as yet unutilized) to "access a settlement agreement upon written request, payment of a specified fee, and with a showing of good cause." *Id.*; 35 U.S.C. § 317(b) ("At the request of a party to the proceeding, the agreement or understanding shall be treated as business confidential information, shall be kept separate from the file of the involved patents, and shall be made available only to Federal Government agencies on written request, or to any person on a showing of good cause.").

209. As of the date of this Article, there have been two settlements between a biologic and prospective biosimilar. On March 13, 2017, Mylan agreed to settle ongoing disputes with Genentech and Roche over its recently filed application to market a biosimilar version of Herceptin. *Mylan Announces Global Settlement and License Agreements with Genentech and Roche on Herceptin*, PR NEWSWIRE (Mar. 13, 2017, 8:00 AM), http://www.prnewswire.com/news-releases/mylan-announces-global-settlement-and-license-agreements-with-genentech-and-roche-on-herceptin-300422255.html. According to the parties, the agreement calls for (1) an exclusive global license allowing Mylan to market its Herceptin biosimilar in various markets around the world and (2) Mylan's withdrawal of two pending IPR petitions against U.S. Patent Nos. 6,407,213 and 6,331,415, both owned by Genentech. Each of the patents appears to claim fundamental methods of making antibodies and would presumably be infringed by a biosimilar maker. Indeed, the '415 patent—commonly referred to as the "Cabilly II Patent"—is one of the most litigated patents of all time and is currently licensed to approximately 70 companies. *See* Charlene Choi & Irena Royzman, *Four Years of IPRs: Lessons from Proceedings for the Cabilly II Patent*, BIOLOGICS BLOG (Sept. 20, 2016), https://www.biologicsblog.com/four-years-iprs-lessons-proceedings-cabilly-ii-patent/. While no entry date for Mylan's proposed biosimilar was announced, based on their date of issuance, the '213 and '415 patents would appear to expire in 2019 and 2018 respectively.

In a second settlement, reached in September 2017, biologic manufacturer AbbVie agreed to drop litigation on arthritis-treating Humira against biosimilar maker Amgen for its Amgevita product. Lisa Schencker, *AbbVie Protects Blockbuster Drug Humira for 5 Years Through Settlement*, CHI. TRIB. (Sept. 28, 2017, 4:35 PM), http://www.chicagotribune.com/business/ct-biz-abbvie-settles-over-humira-092917-story.html. The settlement provides that AbbVie will grant Amgen patent licenses to begin selling its product in the U.S. in 2023 (and in Europe in 2018). *Id.*

uct."[210] And because a biosimilar's manufacturing processes are proprietary trade secrets,[211] applicants could be tempted to enter into settlements to avoid disclosing sensitive information.[212]

In conclusion, factors point in both directions on the likelihood of settlements in the biologics setting. But on balance, given the (1) modest price erosion from biosimilar entry, (2) lasting first-mover advantage available to biologics, and (3) use of the IPR process to challenge biologic patents, we believe there will be fewer settlements than have occurred under the Hatch-Waxman Act. As a final observation, the *Actavis* decision itself likely has reduced, and will continue to reduce, the frequency of reverse-payment settlements.[213]

b. Assessment

In determining the appropriate antitrust analysis of settlements, an initial question centers on the application of *FTC v. Actavis*.[214] We believe that, in a broad holding of general applicability, *Actavis* confirmed antitrust law's vital role in evaluating the legality of settlements involving payment and delayed entry.[215] The Court relied on an array of previous cases[216] to confirm that its precedents "make clear that patent-related settlements can sometimes violate the antitrust laws."[217]

To be sure, the Court was not offering an antitrust assessment of biologic settlements. Nor could it have given that no court—even now, several years later—has considered settlements under the BPCIA. But we believe the setting of complex pharmaceutical regulation under the BPCIA easily offers sufficient similarities to the Hatch-Waxman Act to allow application of *Actavis*'s broad principles.[218] In addition, payment to avoid the risk of biosimilar competition presents the same concerns highlighted in *Actavis*.

The linchpin in the antitrust analysis of settlements is whether a generic is excluded from the market based on a patent or payment.[219] Exclusion based on a patent generally does not present antitrust concern because it is commonly understood that *patent-term split agreements*, by which brands and generics divide the remaining patent term by selecting a time for generic entry, do not violate the antitrust laws.[220] The reason is that the parties' compromise on the

210. 42 U.S.C. § 262(1)(2)(A) (2012).

211. W. Nicholson Price II & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars?* 348 SCIENCE 188 (Apr. 10, 2015), http://science.sciencemag.org/content/348/6231/188.

212. 42 U.S.C. § 262(k)(1); *see generally* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologic Competition and Innovation*, 101 IOWA L. REV. 1023 (2016); Price, *supra* note 50 (discussing the role trade secrets play in developing biosimilars).

213. *See* FTC, BUREAU OF COMPETITION, OVERVIEW OF AGREEMENTS FILED IN FY 2015 (2017) (noting the decline in "potential pay for delay" settlements from 40 in FY 2012 to 14 in FY 2015).

214. 133 S. Ct. 2223, 2227 (2013).

215. *See supra* note 179 and accompanying text.

216. *Actavis*, 133 S. Ct. at 2230–34.

217. *Id.* at 2232.

218. *See* Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 554 (2011).

219. *See generally* Michael A. Carrier, *Payment After* Actavis, 100 IOWA L. REV. 7, 16–18 (2014).

220. *E.g.*, *Actavis*, 133 S. Ct. at 2234.

entry date reflects the odds of success in patent litigation.[221] The greater the likelihood the patent is valid and infringed, the later in the period generic entry would be expected. The lower the likelihood, the earlier entry would be expected. A brand, however, is likely to gain additional exclusivity not explained by a patent by supplementing the parties' entry-date agreement with a payment to the generic.

The same distinction between patent and payment should apply in the setting of biologics. The biologic manufacturer is entitled to rely on its patent to exclude a generic. But it should not be able to pay a biosimilar to gain additional delay.

In determining whether there is payment, the court should consider, as one of us has explained before, whether the biologic manufacturer conveys "a type of consideration not available as a direct consequence of winning the lawsuit."[222] If the biosimilar manufacturer is able to obtain such consideration, "its exclusion from the market cannot be traced to the strength of the [biologic] patent."[223] In such a case, "the [biologic maker] is providing compensation beyond what even a valid and infringed patent would justify."[224] And, presenting antitrust concern, the biosimilar delays entering the market because of this payment.[225]

One example of a form of payment that could arise in this setting involves a biosimilar's access to a biologic's distribution or reimbursement networks. In contrast to distribution through wholesalers and specialty distributors (each of which obtains a portion of revenues, reducing a biosimilar's profitability), biologics could offer access to a "manufacturer direct" channel which, in selling directly to purchasers (*e.g.*, specialty pharmacies and large hospitals), removes the "middleman."[226] Setting up an efficient supply chain is difficult and expensive, and not all biologics will be able to implement such a scheme.[227] As a result, if a biologic has already set up direct distribution, one form of payment to a biosimilar could be access to, and integration into, the valuable network, which it would not be able to obtain through patent litigation.

Another type of payment could involve Group Purchasing Organizations ("GPOs") or Pharmacy Benefit Managers ("PBMs"). GPOs are collections of providers that pool resources to maximize economies of scale in drug purchasing and sometimes function as distributors, gaining control over products offered to downstream purchasers.[228] PBMs also manage prescription drug pro-

221. HERBERT HOVENKAMP, MARK D. JANIS, MARK A. LEMLEY, CHRISTOPHER R. LESLIE, & MICHAEL A. CARRIER, IP AND ANTITRUST: AN ANALYSIS OF ANTITRUST PRINCIPLES APPLIED TO INTELLECTUAL PROPERTY LAW § 16.01[f] (3d ed. 2016).

222. Carrier, *Payment After* Actavis, *supra* note 219, at 9.

223. *Id.*

224. *Id.*

225. *Id.*

226. NIAZI, *supra* note 21, at 354–56; *see also* Jack McCain, *Connecting Patients with Specialty Products*, BIOTECHNOLOGY HEALTHCARE, Summer 2012, at 8, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411231/.

227. NIAZI, supra note 21, at 354–56.

228. *Id.* at 352, 353.

grams for downstream buyers and, in some cases, after negotiating rebates with manufacturers, limit the drugs sold under their plans.[229] This latter role ensures that they "are very important" to a biosimilar manufacturer in controlling access to a biosimilar product.[230] We envision a scenario by which a settlement could include payment in the form of a biologic bringing a biosimilar under its umbrella, granting access to certain GPO and PBM agreements to which it would otherwise not have access.

Where there is payment, the court should consider its size. The *Actavis* Court compared the payment's size to litigation costs.[231] It stated that payments that "amount to no more than a rough approximation of the litigation expenses saved through the settlement" could be justified.[232] Litigation costs in the biologics setting will generally be higher than in the small-molecule setting. In contrast to litigation in the Hatch-Waxman setting, with a generic in the initial stage only needing to review the Orange Book, law firms must conduct substantial pre-application investigations to identify patents that could be raised in the patent dance.[233]

Finally, where there is at-risk entry, a settlement could include a "payment" from the biologic to the biosimilar, but that payment could constitute a legitimate forgiveness of damages.[234] This presents a nuanced case that could be explained by the results of patent litigation. In other words, if the biologic wins, it is entitled to recover damages from the biosimilar. But if the biosimilar wins, it will not be required to pay anything. As a result, a biologic firm's partial waiver of damages that the biosimilar could have owed falls within the range of what the latter could have obtained through successful litigation.[235]

In short, just like it has done in the Hatch-Waxman setting, the distinction between patent and payment can provide an appropriate framework for the antitrust analysis of settlements between biologics and biosimilars.

B. Product Hopping

Product hopping occurs when a manufacturer switches from one version of a drug (say, capsule) to another (say, tablet). Many switches do not raise anticompetitive concern because they offer legitimate benefits and the manufacturer continues to promote the original version.[236] But sometimes the manufacturer undertakes activity, like switching its prescription base from a profitable

229. *Id.* at 351.

230. *Id.*

231. FTC v. Actavis, Inc., 133 S. Ct. 2223, 2236 (2013).

232. *Id.*

233. *See* Carol Pitzel Cruz, Knobbe Martens Partner, Presentation at 24th C5 Forum on Biotech Patenting 2013, The Red Flags Every Patent Attorney Needs to Know to Successfully Navigate the Regulatory Landscape for Biosimilars (Mar. 14, 2013), http://www.slideshare.net/knobbemartens/us-biosimilars-red-flags-for-patent-attorneys. Costs also would tend to be higher because they would be more likely to include IPR proceedings. While the use of IPR challenges is playing an increasing role in the small-molecule setting, it is still not as ubiquitous as it is for biosimilars. *See* Noyes, *supra* note 204.

234. Carrier, *Payment After* Actavis, *supra* note 219, at 44–47.

235. *Id.*

236. *See generally* Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167, 168 (2016).

drug to a modestly changed version, that only makes sense as a stalling tactic to delay a follow-on's entry. This Section shows how biologics' differing science, markets, and regulations suggest a reduced frequency of product hopping but still require robust antitrust analysis.

1. Small Molecules

Brand firms have frequently employed product hopping in the small-molecule setting. Not only has generic entry resulted in dramatic price reductions,[237] but brands have also benefited from a relative ease of reformulations and regulations that pave the way for delay.

Reformulating a small-molecule drug often is not a significant undertaking.[238] As discussed above,[239] small molecules are forged through chemical synthesis, a series of chemical reactions resulting in a final product.[240] This process is predictable, which facilitates reformulation as well as low-cost generic piggybacking. The various types of product hopping reveal the ease of reformulations. One category involves new forms, which consist of switches from a capsule, tablet, injectable, solution, suspension, or syrup to another form, such as any of the above, as well as extended-release capsules or tablets, orally dissolving tablets, and chewable tablets.[241] A second type involves changing molecule parts, known as "moieties."[242] A third category involves a combination of two or more drug compositions that had previously been marketed separately.[243]

Not only do these reformulations tend to be straightforward to accomplish but they also can garner protection through additional patents and FDA exclusivity, as well as the blocking of automatic generic substitution.[244] First, reformulations can benefit from new patent protection. One example is provided by the manufacturer in *Walgreen Co. v. AstraZeneca Pharmaceuticals*, which converted the market from heartburn drug Prilosec to Nexium.[245] Even though the plaintiffs alleged that there was "almost no difference" between the

237. *See supra* notes 106–09 (discussing price reductions); *supra* notes 112–16 (discussing state substitution laws).

238. Carrier & Shadowen, *supra* note 236, at 172.

239. *See supra* note 38 and accompanying text.

240. BORDEN, *supra* note 4, § C:5.1.

241. Steve D. Shadowen et al., *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 RUTGERS L.J. 1, 24 (2009); *see id.* at 37 (offering examples of antidepressant Prozac and cholesterol treatment TriCor switching from capsule to tablet, and anxiety-treating Buspar switching from tablet to capsule).

242. *See id.* at 38 (offering example of switch from heartburn-treating Prilosec to Nexium and chemical-change switches from allergy medication Claritin to Clarinex, antidepressant Celexa to Lexapro, and heartburn-treating Prevacid to Kapidex).

243. *Id.* at 25; *see also id.* at 38–41 (offering combinations of migraine-treatment Treximet (combining Imitrex and Naproxen Sodium) and high-blood-pressure medications Azor (Norvasc and Benicar), Caduet (Norvasc and Lipitor), and Exforge (Norvasc and Diovan)).

244. *See, e.g.*, Eric K. Steffe et al., *The Impact of Reformulation Strategies on Pharmaceuticals, Biologics*, BIOPROCESS ONLINE (Mar. 14, 2016), https://www.bioprocessonline.com/doc/the-impact-of-reformulation-strategies-on-pharmaceuticals-biologics-0001?sectionCode=Editorial&templateCode=Single&vm_tId=1887459.

245. 534 F. Supp. 2d 146 (D.D.C. 2008).

drugs and there was "no pharmacodynamic reason" for the switch, the new version offered an additional thirteen years of patent protection.[246]

A second form of exclusion implicated by product hopping comes from FDA-based market exclusivity.[247] A company receives four or five years of exclusivity for drugs with a new active ingredient[248] and three years for new clinical investigations,[249] which includes new dosage forms, new uses, and adoption of over-the-counter status.[250] Third, even absent patent protection or FDA exclusivity, brand reformulations can delay entry for years until the generic is able to reformulate the product and receive FDA approval.[251] Fourth, in the Hatch-Waxman setting, and as discussed above,[252] reformulations delay entry by avoiding state substitution laws, which require showings of bioequivalence and therapeutic equivalence,[253] and which can be circumvented by reformulation.

2. Biologics

Product hopping is less likely to occur in the biologics setting. But when it does occur, courts should apply an antitrust analysis that incorporates industry realities by applying a no-economic-sense test with a safe harbor based on timing.

a. Likelihood

For three primary reasons, manufacturers are less likely to employ product hopping in the biologics setting. The first reason stems from the science. In contrast to the straightforward reformulations that characterize small-molecule drugs, biologics are larger and more complex,[254] which reduces the frequency of reformulations. As discussed above, developing a biologic molecule can be unpredictable, present challenges for biosimilars greater than those facing manufacturers, and offer difficulties even in analyzing the structure of proteins.[255] Biologics are manufactured in highly complex living systems, with

246. *Id.* at 149; *see also* New York *ex rel.* Schneiderman v. Actavis PLC (Namenda), 787 F.3d 638, 642 (2d Cir. 2015) (brand sought 14 additional years of patent protection by switching Alzheimer's drugs).

247. *See supra* notes 100–02 and accompanying text.

248. 21 U.S.C. §355(j)(5)(F)(ii)) (2012). The exclusivity period is 4 years for generic filers certifying patent invalidity or noninfringement and 5 years for other generic filers. *Id.* And because the agency cannot receive generic applications during this period, the practical exclusivity period is extended by another 2 years, the time it typically takes the FDA to approve an application. THOMAS, *supra* note 92, at 350.

249. 21 U.S.C. §355(c)(3)(E)(iii) (2012).

250. 35 U.S.C. §§ 156(c), (g)(6) (2012); *see generally* Carrier, *Unsettling Drug Patent Settlements*, *supra* note 82, at 44.

251. Carrier, *A Real-World Analysis*, *supra* note 112, at 1018.

252. *See supra* notes 115–16 and accompanying text.

253. *See* FDA, *Orange Book*, *supra* note 93.

254. *See supra* notes 32–52 and accompanying text.

255. *See supra* notes 32–52 and accompanying text.

slight changes potentially resulting in structural alterations or system contaminations leading to immunogenicity issues.[256]

The second reason to expect fewer product hops stems from the markets, with follow-on biosimilars not being the same as the original product. Unlike generic versions of small-molecule drugs, which are chemically identical to the brand versions, the structural variability and complexity inherent in biologic development cause follow-on versions to strive only for similarity.[257] Relatedly, the difficulty in manufacturing biologics helps explain prices higher than they are in the small-molecule setting.[258] These development costs and lack of identity between biologics and biosimilars make it less likely that the market will experience the dramatic price reductions that have been observed in the small-molecule setting and that have motivated product hopping.

The third reason stems from the regulatory regimes. The BPCIA allows for only *one* 12-year period of exclusivity for each drug,[259] with a possible 6 additional months based on pediatric exclusivity.[260] In contrast to the Hatch-Waxman Act, which allows brands to obtain *multiple* forms of exclusivity, including those relating to new active ingredients, new clinical trials, new dosages, and pediatric exclusivity,[261] the BPCIA does not provide additional regulatory exclusivity for (1) changes resulting in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength or (2) modifications to a biological product's structure not resulting in a change in safety, purity, or potency.[262] By not offering additional exclusivity periods—which are stronger than patents in preventing the agency from receiving or granting applications[263]—the regulatory structure offers less incentive to engage in product hopping.

In fact, unlike reformulations in small molecules, biologic manufacturers likely will be required to redo clinical trials and conduct new studies to obtain a new 12-year exclusivity period.[264] Although product-hopping cases do not always involve drugs for which the brand firm has received regulatory exclusivity, this factor supports a modestly reduced incentive to make inconsequential product changes. A biologic manufacturer also should experience less ur-

256. Steffe, *supra* note 244; FDA, *Immunogenicity of Protein-Base Therapeutics* (Feb. 29, 2016), http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/BiologicsResearchAreas/ucm246804.htm. For a discussion of immunogenicity, see *supra* notes 46–49 and accompanying text.

257. *See* JUDITH A. JOHNSON, CRS, R44620: BIOLOGICS AND BIOSIMILARS: BACKGROUND AND KEY ISSUES 1 (2016).

258. *See supra* Section II.B.

259. 42 U.S.C. § 262(k)(7) (2012).

260. *Id.* § 262(m).

261. *See supra* notes 245–47 and accompanying text.

262. 42 U.S.C. § 262(k)(7)(C)(ii) (2012); *see also* FDA, REFERENCE PRODUCT EXCLUSIVITY FOR BIOLOGICAL PRODUCTS FILED UNDER SECTION 351(A) OF THE PHS ACT: GUIDE FOR INDUSTRY (2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf. After adopting the 12-year exclusivity period, stakeholders initially contemplated additional 12-year periods for supplements and applications to new conditions of use such as new indications, routes of administration, dosage forms, or strengths for previously licensed reference products. In July 2009, the Senate Committee on Health, Employment, Labor and Pensions rejected such potential extensions. Lietzan, *supra* note 80, at 19–20.

263. *See supra* notes 125–26 and accompanying text.

264. Lietzan, *supra* note 80, at 18–22.

gency to switch the market to a reformulated version because of the absence of state substitution laws, which could have shifted the emphasis from biosimilar marketing to price-conscious pharmacists.[265]

In short, the frequency of brand reformulations likely will be reduced. But to the extent switches will occur, past experience reveals that they are more likely to be based on innovation that makes economic sense regardless of the effect on competition.

One example of a recent reformulation has occurred in the class of biologics treating neutropenia (low white-blood-cell count after chemotherapy).[266] Amgen's Neupogen, a first-generation biologic approved in 1991, helps a patient recover white blood cells after chemotherapy.[267] This is critical because low white-blood-cell counts could plague a patient for an extended period, leading to decreased immune response and infections such as hepatitis or inflammation-inducing sepsis.[268] Neupogen is administered daily after chemotherapy for up to 10 days, which requires patients to administer the drug themselves or repeatedly return to the doctor's office.[269] First marketed as an injectable solution dispensed in a vial with an empty syringe, Neupogen is now also available as a prefilled syringe.[270]

In light of Neupogen's success, Amgen in 2002 introduced longer-lasting Neulasta.[271] Unlike Neupogen, which requires daily administration because its half-life in a patient's body is only 3.5 hours, Neulasta stays in the body for 80 hours.[272] As a result, Neulasta has been a major success, with global annual

265. *See supra* notes 112–14 and accompanying text. Although interchangeable biosimilars would be subject to substitution, there have not yet been any and, for the reasons we discuss above, see *supra* notes 138–40 and accompanying text, we expect the majority of follow-on biologics to seek biosimilar status alone rather than interchangeability.

266. *Symptoms Neutropenia (Low Neutrophil Count)*, MAYO CLINIC (Jan. 16, 2006), http://www.mayoclinic.org/symptoms/neutropenia/basics/definition/sym-20050854 For another example, manufacturers of Rituxan have switched from intravenous ("IV") infusion (directly into a vein) to subcutaneous (applied under the skin) formulations, which can result in easier administration for patients. Steffe et al., *supra* note 244 (discussing Herceptin and Rituxan reformulations in Europe). And, while reformulation efforts involving oral administration have proven unsuccessful, Phil Taylor, *Oral Biologics Delivery Still Elusive*, PMLIVE (Feb. 17, 2016), http://www.pmlive.com/pharma_intelligence/oral_biologics_delivery_still_elusive_908436, the industry continues researching new modes of administration, such as inhaled formulations, *e.g.*, Randi Hernandez, *Intertek Explores the Reformulation of Intravenous Biologics*, BIOPHARM INT'L (Dec. 4, 2015), http://www.biopharminternational.com/intertek-explores-reformulation-intravenous-biologics.

267. *Filgrastim: Dosing & Uses*, MEDSCAPE, http://reference.medscape.com/drug/g-csf-neupogen-filgrastim-342164 (last visited Nov. 4, 2017).

268. *Neutropenia (Low Neutrophil Count)*, MAYO CLINIC (Jan. 20, 2016) [hereinafter *Neutropenia*], http://www.mayoclinic.org/symptoms/neutropenia/basics/causes/sym-20050854.

269. *See* MEDSCAPE, *supra* note 267.

270. *Neutropenia*, *supra* note 268.

271. Jay P. Siegel, Dir. Office of Therapeutics Research & Review, Ctr. for Biologics Eval. & Research, to Jeffrey N. Fellows, Amgen, Inc. (Jan. 21, 2002) (providing FDA approval for Pegfilgrastim), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/pegfamg0131102l.htm.

272. *Filgrastim*, DRUGS.com, https://www.drugs.com/ppa/filgrastim-g-csf.html; *Pegfilgrastim (Rx)*, MEDSCAPE, http://reference.medscape.com/drug/neulasta-pegfilgrastim-342167#10 (last visited Nov. 11, 2017); Thomas A. M. Kramer, *Side Effects and Therapeutic Effects*, 5(1) MEDSCAPE GEN. MED. (2003), http://www.medscape.com/viewarticle/448250_3 (last visited Nov. 11, 2017) ("medications vary in how long it takes to clear them from the body," with "the term 'half-life' [referring to] how long it takes for the body to get rid of half of the dose").

sales of $4.4 billion.[273] In addition, Neulasta, which was initially sold as a prefilled syringe, is now also available as a prefilled on-body patch that automatically injects the patient at a preset time.[274] With this new on-body patch delivery mechanism, patients who have just undergone chemotherapy need not immediately return to the doctor's office or administer the prefilled syringe. In short, the switches from (1) daily Neupogen to long-lasting Neulasta and (2) prefilled syringe Neulasta to on-body injector patch Neulasta offer material benefits for patients.

b. Assessment

Given the reduced likelihood of biologic product hopping, courts are less likely to confront the antitrust implications of the conduct. But when they do, they can apply an improved version of the antitrust analysis they have developed in the small-molecule setting, evaluating a no-economic-sense test and timing-based safe harbor that incorporates the realities of the pharmaceutical industry.

In analyzing the antitrust effects of product hopping, courts have distinguished between "hard switches" (in which the brand removes the original version from the market) and "soft switches" (in which the brand leaves the original version on the market). In the former case, they have concluded that the removal of the original drug forces the patient to purchase the reformulated version.[275] In the latter, they have claimed that the patient has a choice between the drugs.[276] The courts are correct in finding that hard switches often violate the antitrust laws since, in many cases, the behavior only makes sense by harming generic competition.

But in allowing soft switches, courts have been excessively lenient. The reason stems from the complexity of the markets, with the buyer (patient, GPO, or insurance company) differing from the decision-maker (doctor).[277] This disconnect encourages brands to switch their heavy marketing and promotion efforts to the reformulated version, even if such behavior makes sense only by reducing demand for the still-profitable original version. In other words, the only reason for certain soft switches is to harm generics.

Rather than imbuing dispositive effect to whether the switch is "hard" or "soft," courts could apply a no-economic-sense test that asks whether conduct allegedly maintaining a monopoly by excluding nascent competition likely would have been profitable if such competition flourished and the monopoly was not maintained.[278] Such an inquiry offers an economic test that determines

273. Carly Helfand, *Neulasta*, FIERCEPHARMA, http://www.fiercepharma.com/special-report/Neulasta (last visited Nov. 14, 2017) (reporting figures from 2013).

274. Press Release, Amgen, Amgen Announces Launch of New Neulasta® (Pegfilgrastim) Delivery Kit (Mar. 2, 2015), http://www.prnewswire.com/news-releases/amgen-announces-launch-of-new-neulasta-pegfilgrastim-delivery-kit-300043818.html.

275. New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 659 (2d Cir. 2015).

276. Walgreen Co. v. AstraZeneca Pharms., 534 F. Supp. 2d 146, 151 (D.D.C. 2008).

277. DRUG PRODUCT SELECTION REPORT, *supra* note 113, at 2–3.

278. Gregory J. Werden, *Identifying Exclusionary Conduct Under Section 2: The "No Economic Sense" Test*, 73 ANTITRUST L.J. 413, 415 (2006).

whether a monopolist's sole motive is to impair competition. If a firm engages in behavior that makes no economic sense, then its "anticompetitive intent" can be "unambiguously . . . inferred."[279] In settings other than product hopping, many courts, including the Supreme Court, have adopted the no-economic-sense test (or related profit-sacrifice test[280]).

One example of how the test could be applied is presented by Amgen's switches from Neupogen to Neulasta and from prefilled syringes to on-body injectors. First, while Neupogen continues to be an effective cancer therapy, Amgen's introduction of the longer-lasting Neulasta in 2002 offered material improvements in allowing chemotherapy patients to avoid trips to the doctor's office that would reasonably appear to garner enough additional sales to justify the research-and-development ("R&D") expense.[281] Relatedly, because competition between biologics and biosimilars promises to resemble competition between brands in the small-molecule context,[282] it is more likely that changes will offer actual improvements in competing against independent rivals.

Second, as to the switch within the Neulasta product line, Amgen's subsequent introduction of on-body patches also offered a benefit that made economic sense regardless of its effect on biosimilar competition. For years, Neulasta was available in prefilled syringes that could be administered by a nonprofessional caregiver.[283] But that raised patient-compliance issues. The switch to an automatic on-body injector worn at home potentially reduces mistakes and improves drug administration to an extent that would appear to be worth the investment.[284]

Our proposed framework benefits biologic manufacturers not only through the application of the defendant-friendly, no-economic-sense test but also through a safe harbor based on the timing of reformulation. Manufacturers should not confront antitrust liability if a biosimilar enters the market *before* the manufacturer introduces its reformulated version because in that case it will be less likely to block follow-on entry.[285] In the Hatch-Waxman setting, brands have been successful in using their heavy promotion and marketing artillery to convince doctors to prescribe their reformulated drug when there is not yet a generic on the market. If the brand successfully switches the market to the re-

279. A. Douglas Melamed, *Exclusive Dealing Agreements and Other Exclusionary Conduct—Are There Unifying Principles?*, 73 ANTITRUST L.J. 375, 393 (2006).

280. The profit-sacrifice test offers a more aggressive test that may not credit short-term profit sacrifice even for long-term economic gain.

281. *See supra* notes 271–73 and accompanying text.

282. Press Release, Fed. Trade Comm'n, FTC Releases Report on Follow-on Biologic Drug Competition (June 10, 2009), https://www.ftc.gov/news-events/press-releases/2009/06/ftc-releases-report-follow-biologic-drug-competition.

283. Varun Saxena, *Amgen Launches Delivery Device for Automatic Administration of its Blockbuster Neulasta*, FIERCEPHARMA (Mar. 4, 2015), http://www.fiercepharma.com/r-d/amgen-launches-delivery-device-for-automatic-administration-of-its-blockbuster-neulasta.

284. Tara Arvedson et al., *Design Rationale and Development Approach for Pegfilgrastrim as a Long-Acting Granulocyte Colony-Stimulating Factor*, BIODRUGS, May 2015, at 185, 195, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4488452/.

285. *See* Shadowen et al., *supra* note 241, at 51 (explaining how introduction of reformulation before generic entry prevents nearly all competition on price and quality).

formulated version before the generic enters, entry tends to have limited practical effect since there will be little demand for the original product.[286]

Examples demonstrate the crucial role of timing, in particular the brand's recognition of its dramatically higher success if it can switch the market to the reformulated drug before a generic version of the original product enters the market. In *Abbott Laboratories v. Teva Pharmaceuticals* (*TriCor*), the brand predicted that it would sell more than *ten times* as many tablets if it was able to switch doctors to the reformulated product before the generic version of the original entered the market.[287] Another brand firm acknowledged that "its reformulation was 'a gimmick' and that switching the market before generic entry was the 'cardinal' determinant of success."[288]

Although the price and market-penetration effects of follow-on biosimilar competition are less direct, the timing issue is still critical. For if the biologic manufacturer can migrate the market before the biosimilar enters, doctors who have switched to the reformulated version are less likely to switch back.[289] In short, the application of the no-economic-sense test and safe harbor promises to create a deferential framework rooted in the realities of the biologics industry. Though product hopping should not occur as frequently in the biologics setting, the framework articulated in this Section should support most of the reformulations while ensuring rigorous scrutiny for the most concerning switches.

C. Regulatory Abuse

Product hopping's roadblocks in the path of follow-on competition are compounded by additional conduct that exploits the regime to further delay entry. As discussed above,[290] the BPCIA consists of a complex set of regulations to promote competition and innovation. And just as brand firms have violated the antitrust laws by exploiting the Hatch-Waxman Act, so too do biologic manufacturers appear to be starting to use patent thickets and complex patent continuation practices[291] to thwart biosimilar entrants.[292] This Section exam-

286. *See* Carrier & Shadowen, *supra* note 236, at 176–77.

287. Shadowen et al., *supra* note 241, at 52.

288. *Id.* at 53; *see also* New York *ex rel.* Schneiderman v. Actavis PLC, 787 F.3d 638, 656 (2d Cir. 2015) (quoting defendant executive who stated that if brand "do[es] the hard switch and . . . convert[s] patients and caregivers to once-a-day therapy versus twice a day, it's very difficult for the generics then to reverse-commute back"); Meijer, Inc. v. Barr Pharm., Inc., 572 F. Supp. 2d 38, 43 (D.D.C. 2008) (explaining why some view it as a "[t]otal [d]isaster" if reformulated product introduced after generic of original entered market); AARON GAL, WHY DOES LIFECYCLE MANAGEMENT STILL WORK? 3 (June 14, 2013) (empirical review of product hops concludes that "after a patient is on the new drug and the old drug has gone generic, the new brand did not lose share").

289. *E.g.*, Jorge Cortes et al., *Expert Perspectives on Biosimilar Monoclonal Antibodies in Breast Cancer*, 144 BREAST CANCER RES. TREATMENT 233, 238 (2014) (switching between biologics and biosimilars "with or without the physician's consent should be avoided"); *see also* New York v. Actavis, 787 F.3d at 656 ("Although in theory, Alzheimer's patients would be free to switch back to [the original version] after generic entry, the district court found that, in practice, such a reverse commute would be a highly unlikely occurrence.").

290. *See supra* Section III.B.

291. *See* Mark A. Lemley & Kimberly A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. REV. 63, 69 (2004).

ines how manufacturers could manipulate "Phase 2" BPCIA litigation and how antitrust law should address these anticompetitive practices.

1. Hatch-Waxman Act

In many ways, the Hatch-Waxman Act has been successful. Generic drugs, which made up only 19% of prescriptions for drug products in 1984,[293] increased to 88% by 2015.[294] At the same time, however, the law created a complex framework that brands have exploited to delay generic competition. As discussed above,[295] one behavior that has received significant attention involves settlements by which brands have paid generics to delay entering the market.

Another activity involves the manipulation of provisions designed to channel parties to litigation through patent listings.[296] The process begins when a brand, after receiving FDA approval, lists a patent in the Orange Book.[297] A generic then files an ANDA, notifying the brand through a Paragraph IV certification that the listed patent is invalid or not infringed, after which the brand files suit, triggering an automatic 30-month stay of FDA approval.[298]

Although the 30-month stay was anticipated to provide protection for the period mirroring the periods of FDA approval and litigation,[299] such protection could be justified based on only single stays. Until 2004, however, by prosecuting and obtaining patents beyond those listed in the Orange Book when the FDA first approved the product, brands could obtain multiple 30-month stays against generics.[300] One example of this tactic, known as *evergreening*, was offered by GlaxoSmithKline, which obtained multiple 30-month stays and blocked generic competition on antidepressant Paxil for more than five years.[301] In response to this behavior, Congress included a provision in the 2003 Medicare amendments that limited stays to patents provided to the FDA before the ANDA submission, essentially limiting companies to one 30-month stay.[302]

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292. *See* Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Entry*, N.Y. TIMES (July 15, 2016), https://www.nytimes.com/2016/07/16/business/makers-of-humira-and-enbrel-using-new-drug-patents-to-delay-generic-versions.html.

293. *Generic Pharmaceuticals: Marketplace Access and Consumer Issues: Hearing Before the S. Comm. on Commerce, Sci., & Transp.*, 107th Cong. 72 (2002) (statement of Kathleen D. Jaeger, President and CEO, Generic Pharmaceutical Association).

294. GPHA, GENERIC DRUG SAVINGS, *supra* note 108, at 1.

295. *See supra* notes 170–85 and accompanying text.

296. THOMAS, *supra* note 92, at 346–52.

297. FDA, *Orange Book*, *supra* note 93.

298. 21 U.S.C. §355(j)(5)(B)(iii) (2012).

299. *See* FTC, GENERIC DRUG STUDY, *supra* note 90, at 39 (noting that 30-month stay approximates 25-month periods for (1) FDA approval of generic applicants filing Paragraph IV certifications that are not sued and (2) average period between filing of complaint and district court decision).

300. *See* HOVENKAMP, JANIS, LEMLEY, LESLIE, & CARRIER, *supra* note 221, § 15.3; Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368, 1376 (Fed. Cir. 2002).

301. FTC, GENERIC DRUG STUDY, *supra* note 90, at 51.

302. 21 U.S.C. §355(j)(5)(B)(iii). *See generally* Carrier, *supra* note 82, at 47–48; *see id.* at 48 (noting that multiple 30-month stays are still possible if generic files Paragraph III and Paragraph IV certifications on different patents and then, before ANDA submission, changes Paragraph III designation to Paragraph IV).

In the context of multiple 30-month stays, the case of *In re Neurontin Antitrust Litigation*[303] highlights the antitrust implications of regulatory abuse through the filing and dismissal of continuation applications at the Patent Office. The plaintiffs alleged that "[r]ather than aggressively prosecuting the patent," the brand "took great pains to prolong the continued prosecution . . . so that the patent issued at a time when the 30-month stay . . . could be used to further delay generic competition."[304] The court rejected the brand's contention that its prosecution was immune from antitrust liability under the *Noerr-Pennington*[305] doctrine protecting government petitioning.[306]

The *Neurontin* court held that an exception to immunity for sham conduct[307] applied because the plaintiffs alleged that the brand had "manipulated" patent protection "to delay its issuance and thereby forestall generic competition . . . by obtaining 30-month stays barring generic products from the market."[308] In particular, the brand "withheld prior art, filed unnecessary continuation applications, and abandoned an approved patent application . . . to obtain successive, rather than concurrent, 30-month stays."[309] The court recognized that "[t]he Hatch-Waxman regulatory scheme presents unique opportunities for gamesmanship by offering a 'non-refundable' 30-month stay" and that "[f]raudulently delaying the issuance of a patent could lead to anticompetitive effects."[310] "Abuse of the Patent Office's administrative and regulatory process," the court concluded, "is not entitled to immunity."[311]

The fraudulent listing of patents in the Orange Book constitutes another form of regulatory abuse. Brands have listed patents that claim not the drug at issue but unrelated drugs. When a prospective generic then files an ANDA and submits its Paragraph IV certification, it is stuck litigating a patent for 30 months that may not even apply to the drug at issue.[312] Brands have been able to engage in fraudulent listings since the FDA exercises only a ministerial review role.[313] Such a limited role prevents *Noerr* immunity, which does not apply "where the government does not perform any independent review of the validity of . . . statements" or "issue any intervening judgment, . . . instead act[ing] in direct reliance on the private party's representations."[314] This limited role also increases the importance of antitrust scrutiny.

303. No. 02-1390, 2009 WL 2751029, at *19 (D.N.J. Aug. 28, 2009).

304. *Id.* at *18; *see also* Abraxis Bioscience, Inc. v. Navinta LLC, No. CIV. A. 07-1251 (JAP), 2008 WL 2967034 (D.N.J. July 31, 2008) (allowing antitrust claim to proceed when patent owner improperly delayed listing patents in Orange Book to forestall generic approval).

305. United Mine Workers of Am. v. Pennington, 381 U.S. 657 (1965); E.R.R. Presidents Conference v. Noerr Motor Freight, Inc., 365 U.S. 127 (1961).

306. *Neurontin*, 2009 WL 2750129, at *19.

307. The sham exception covers "an attempt to interfere directly with the business relationships of a competitor." *Noerr*, 365 U.S. at 144.

308. *Neurontin*, 2009 WL 2750129, at *19.

309. *Id.*

310. *Id.* at *20.

311. *Id. See also* DiscoVision Assocs. v. Disc Mfg., Inc., No. CIV. A. 95–21–SLR, 1997 WL 309499, at *8 (D. Del. Apr. 3, 1997) (noting that continuation applications "may form a basis for antitrust liability").

312. *E.g.*, *In re* Buspirone Patent Litig., 185 F. Supp. 2d 363, 375 (S.D.N.Y. 2002).

313. *See* Apotex, Inc. v. Thompson, 347 F.3d 1335, 1349–50 (Fed. Cir. 2003).

314. *In re* Buspirone, 185 F. Supp. 2d at 369–70; *see also In re* Ciprofloxacin Hydrochloride Antitrust Litig., 261 F. Supp. 2d 188, 212–13 (E.D.N.Y. 2003); Watson Pharm., Inc. v. Henney, 194 F. Supp. 2d 442,

As was shown in *Neurontin*, the absence of *Noerr* protection results in courts addressing anticompetitive concerns. The Supreme Court in *Caraco Pharmaceutical Labs v. Novo Nordisk*[315] characterized as "anticompetitive" a brand's use of overbroad listing codes in the Orange Book that were not limited to exclude a generic's noninfringing use.[316] To similar effect, in *In re Remeron Antitrust Litigation*,[317] the brand waited 14 months to list a patent in an apparent effort to delay generic entry despite an FDA regulation requiring patents to be listed in the Orange Book within 30 days of patent issuance.[318] The court held that "[w]ithin the maze of Hatch-Waxman, if a patent-holder's actions unlawfully maintain otherwise lawful monopoly power or use a lawful patent to manipulate the ANDA process, such actions could lead to anticompetitive effects in the relevant market."[319]

The Supreme Court in *Verizon Communications v. Law Offices of Curtis V. Trinko*[320] made clear that, in limiting the role of antitrust analysis, courts must find not only that a regulatory regime exists but also that it functions effectively. In *Trinko*, the Court explained that phone companies that provided local service were required to "be on good behavior" and not to discriminate in providing access to certain facilities before they could enter the long-distance market.[321] In addition, firms that did not satisfy these conditions were subject to financial penalties, daily or weekly reporting requirements, and the suspension or revocation of long-distance approval.[322]

In contrast, in the Hatch-Waxman setting, regulatory abuse has prevented the regime from operating as intended.[323] Behavior like pay-for-delay settlements, multiple 30-month stays, and fraudulent patent listings are textbook examples of a regulatory regime not effectively being enforced, which necessitates a role for antitrust. Because the FDA is not able to address anticompetitive schemes, antitrust law must fill the void.

445 (D. Md. 2001) (FDA, "in deciding to make an Orange Book listing, is not acting as a patent tribunal" as it "has no expertise . . . to determine matters of substantive patent law," which means that "[i]n making its decision to list a patent," it "rel[ies] on the patentee's declaration as to coverage . . . ."); *see generally* HOVENKAMP, JANIS, LEMLEY, LESLIE, & CARRIER, *supra* note 221, § 15.3.

315. 566 U.S. 399 (2012).

316. *Id.* at 408.

317. 335 F. Supp. 2d 522 (D.N.J. 2005).

318. *Id*. (citing 21 C.F.R. § 314.53(c)(2)(ii) (2017)).

319. *Remeron*, 335 F. Supp. 2d at 532.

320. 540 U.S. 398 (2004).

321. *Id.* at 412.

322. *Id.* at 412–14; *see also* Credit Suisse Securities (USA) LLC v. Billing, 551 U.S. 264, 277 (2007) (noting Securities Exchange Commission's active enforcement, as shown through detailed definitions of "what underwriters may and may not do and say during their road shows" and actions against underwriters violating regulations).

323. *See Remeron*, 335 F. Supp. 2d at 531 (distinguishing *Trinko* on grounds that Telecommunications Act of 1996 granted regulators significant power to address abuses, while FDA had only ministerial role, which resulted in absence of "regulatory scheme so extensive as to supplant antitrust laws").

2. BPCIA

Just as the Hatch-Waxman Act's regulatory regime has not always worked as intended, the BPCIA appears to be headed in this direction as well. Until now, this has not received attention. But given that we are on the cusp of a multi-billion-dollar biosimilars market[324] and that (if the Hatch-Waxman setting has revealed anything) a primary hurdle will be biologics' suppression of competition by undermining the BPCIA, attention is immediately needed.

As discussed above,[325] the BPCIA creates two phases of patent litigation.[326] In Phase One, a biologic manufacturer and biosimilar applicant litigate patents identified through the patent dance. This consists of either the patents the parties selected during good-faith negotiations,[327] or (when no agreement is reached) a subset of patents identified through the simultaneous exchange.[328] In Phase Two, the BPCIA allows a biologic manufacturer to file a preliminary injunction on (1) patents included in its initial list of patents but not litigated during Phase One[329] and (2) newly issued or licensed patents obtained after the initial patent list.[330] We believe that the second phase of the BPCIA patent litigation could be subject to significant regulatory abuse.[331]

a. Likelihood

Abuse of the BPCIA's patent provisions threatens harm to competition and market expectations. To be sure, the dangers differ from abuse of the Hatch-Waxman regime with its regulatory windfalls in the form of automatic 30-month stays. Instead, unlike the small-molecule setting, where inappropriate patent listings at least give a generic *some* notice before market entry and immediately after filing, in the world of biologics, abuse of the patent provisions may cause delay *years* after a biosimilar application has been submitted and millions of dollars invested in a dispute that should have been resolved in Phase One. And though some of the anticompetitive effects could dissipate over time, there could be more frequent abuse in the short term.

One of the most fundamental differences between the Hatch-Waxman Act and BPCIA is the lack of an Orange Book for biologics. In the Hatch-Waxman setting, ANDA filers are aware of potential patents that will form the basis for litigation years in advance and are able to (or at least attempt to) develop follow-on products to avoid infringement. In contrast, under the BPCIA, alleged patent protection is identified only after the parties have negotiated

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324. *Sales Revenue for Biosimilars in the U.S. is Expected to be $1.9B in 2015 and Increase to $11B by 2020, Finds New Report*, BIOSIMILAR DEV. (Aug. 12, 2015), https://www.biosimilardevelopment.com/doc/sales-revenue-biosimilars-u-s-is-expected-increase-finds-new-report-0001.

325. *See supra* Subsection III.B.3.

326. BARR, *supra* note 149, § 14:4.6[G].

327. 42 U.S.C. § 262(l)(6)(A) (2012).

328. *Id.* § 262(l)(6)(B).

329. *Id.* § 262(l)(8)(A)–(B) (applying after biosimilar applicant files notice of first commercial marketing).

330. *Id.* § 262(l)(7).

331. There is less chance for abuse of Phase One since both parties are negotiating, in contrast to Phase Two, where it is only the biologic that is deciding whether to add more litigation complexity to the equation.

their way through the patent dance, which occurs long after the development of the follow-on product.[332] Given the lack of Orange-Book-type notice and absence of a list of biologic patents, the BPCIA framework will not lend itself to antitrust claims based on fraudulent listing.

Despite the absence of this form of anticompetitive conduct, the BPCIA could be abused through biologics' assertion of late, hidden patents. Early indications are that biologic manufacturers have been using patent-prosecution tools to thwart biosimilar competition.[333] These tools include not only patent prosecution and thickets but also *submarine patents*, which are generally believed to have disappeared after patent law changes in 1995.[334] Submarine patents involve an applicant's use of silent delay tactics at the PTO, aimed at obtaining issuance of a patent years after the initial filing, but still with the legal right to surprise a mature market.[335] There are a few hundred more submarine applications in the PTO's pipeline yet to work their way through the system,[336] with some of these turning out to be biologic patents.

One example is provided by Amgen's anti-inflammatory drug Enbrel.[337] Two core patents covering the drug were set to expire in 2012 and 2014, and biosimilar entrants identified these patents as representing the end of Amgen's patent protection on the drug.[338] In fact, in 2004, long before the patents expired, Sandoz began developing a follow-on version of Enbrel.[339] But by 2011, immediately before Sandoz planned to submit a biosimilar application under the newly enacted BPCIA, Amgen announced that the PTO had granted two

332. *See* Carl J. Minniti III, *Biosimilar Litigation: The Tussle Over How to Resolve Biologic Patents*, ABA SCITECH L., Spring 2015, at 16, 19 (2015) [hereinafter Minniti, *Biosimilar Litigation*]; *see also* Jenny M. Aslup, Note, *You Can Dance If You Want To? Initial Interpretations of the BPCIA's Patent Dance with Sandoz and Amgen*, 8 HASTINGS SCI. & TECH. L.J. 137, 140 (2016). While biosimilars hire sophisticated patent counsel to identify patents held by the biologic, such pre-suit investigation can pose a substantial burden beyond checking the Orange Book, which is exacerbated by the biosimilar's typical expenditure of at least $200 million on product development.

333. Paul Calvo, *Post-Grant Proceedings Are Important for Biosimilars*, LAW360 (Mar. 19, 2015), https://www.law360.com/articles/629125/post-grant-proceedings-are-important-for-biosimilars ("[C]ompared to their small molecule brethren, biosimilar developers potentially face a much more complicated patent thicket because of the complexity of producing a biologic product.").

334. Lemley & Moore, *supra* note 291, at 80.

335. *See* Mohsenzadeh v. Lee, 5 F. Supp. 2d 791, 795 n.2 (E.D. Va. 2014). Before 1995, when Congress adopted the 1994 Uruguay Round of the General Agreement on Tariffs and Trade ("GATT"), which effectively eliminated submarine patents, applications were secret through the entire application process, resulting in some applicants using continuation practices to prevent the patent from issuing. When the time was right, the applicant would then seek issuance, causing the patent to emerge (like a submarine) from Patent Office secrecy and obtain 17 years of enforceability from the issuance date. *See* Dennis Crouch, *Old-School Submarine Patents*, PATENTLY-O (Dec. 14, 2010), http://patentlyo.com/patent/2010/12/old-school-submarine-patents.html; *see also* Alexander M. Bell, *An Autopsy on Submarine Patents: A Window into Expectation of the World Technological Frontier* 16–18 (Apr. 17, 2013) (unpublished honors thesis, Brown University) (on file with the Brown Univ. Dep't of Econ.), https://www.brown.edu/academics/economics/sites/brown.edu.academics.economics/files/uploads/Bell_Thesis.pdf; *cf.* Lemley & Moore, *supra* note 291, at 80 ("There is no social benefit whatsoever to submarine patents.").

336. Crouch, *supra* note 335, ¶ 3.

337. Complaint for Declaratory Judgment of Patent Invalidity and Non-Infringement at 4–5, Sandoz, Inc. v. Amgen, Inc., No. 13-2904 (N.D. Cal. June 24, 2013).

338. *Id.* at 5.

339. *Id.* at 7.

new patents claiming Enbrel.[340] These two patents turned out to be submarine patents that had been silently percolating in the PTO for *15 years*.[341]

While the Hatch-Waxman Act and BPCIA patent-related provisions differ, both frameworks could form the setting for a late assertion of patent rights. In the same way that manufacturers of small-molecule brand drugs can fraudulently list patents just before the filing of ANDAs,[342] so too can biologic manufacturers assert additional patents during Phase-Two litigation.[343] Given the nonpublic nature of the process, there is potential for considerable harm.

If a biologic manufacturer obtains an additional patent (either through PTO issuance or exclusive licensing) after the initial patent list[344] has been sent to the biosimilar applicant, it may seek a preliminary injunction blocking the manufacture or sale of a biosimilar falling within the scope of the patent.[345] Once the biologic has obtained this additional patent, the BPCIA only requires the manufacturer to "reasonably believe[] that, due to the issuance of such patent," an infringement claim could "reasonably be asserted" against the biosimilar maker.[346]

We think this provision could be exploited in two subtle, though significant, ways. First, as seen in the *Enbrel* case,[347] the biologic manufacturer could employ submarine patents to extend patent protection. The company could proceed through the patent dance and good-faith negotiations, *all while secretly prosecuting the submarine patent*. Then, late in the litigation process (and in contravention of the BPCIA's broad principle of early litigation of relevant patents[348]), it could obtain that patent and seek a preliminary injunction. In fact, while the consensus is that the harmful market effects of submarine patents pose less of a problem since Congress's 1995 amendment to the patent term and publication of applications after 18 months,[349] early biosimilar litigation reveals that these patents can still surprise rivals, causing competitive uncertainty.[350] In the coming decades, this fear will dissipate as submarine patents

340. Press Release, Amgen, Enbrel (Etanercept) Patent Issued (Nov. 22, 2011), http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-newsArticle&ID=1633115; *see also* Andrew Pollack, *Makers of Humira and Enbrel Using New Drug Patents to Delay Generic Versions*, N.Y. TIMES, July 16, 2016, at B1.

341. U.S. Patent Nos. 8,063,182 and 8,163,522 were filed on May 19, 1995 and claim priority to a patent application filed on September 10, 1990. U.S. Patent Application No. 07/580,013. Of note, four applications claiming priority to the '013 application have been patented: two patents issued in 1997 and 1998 and two submarine patents issued in 2011 and 2012.

342. *See supra* notes 312–19 and accompanying text.

343. *See supra* notes 329–30 and accompanying text.

344. 42 U.S.C. § 262(l)(3)(A) (2012).

345. *Id.* § 262(l)(8)(B).

346. *Id.* § 262(l)(7)(B) (requiring biologic sponsor, within 30 days of obtaining new patent, to send supplemental list that includes patent to biosimilar applicant).

347. *See supra* notes 337–41 and accompanying text.

348. *See supra* notes 155, 327; *infra* notes 353–57, 582 and accompanying text.

349. Lemley & Moore, *supra* note 291, at 80.

350. There does not appear to be much legislative history on the issues of submarine patents and patent thickets. But in discussing evergreening and whether incremental changes to a biologic product would receive additional exclusivity (as it would under the Hatch-Waxman Act), Representative Darrell Issa raised the concern, questioning industry representatives on the role patent prosecution practices would play in blocking follow-on competition *after* exclusivity expired. He asked the president of a leading intellectual property association:

make their way through the system. But in the near future, it requires close scrutiny.

Second, a biologic manufacturer could assign a patent to a shell company[351] immediately before or after the submission of a biosimilar application, thereby allowing it to avoid disclosing the patent's existence during the patent dance, good-faith negotiation, and Phase-One litigation. Then, late in the game, the shell company could assign the patent back to the manufacturer, allowing it to pursue a preliminary injunction.[352]

Under both of these scenarios, the manufacturer could avoid the restriction on BPCIA infringement actions to those patents that "should have been included" in the initial exchange pursuant to the patent dance.[353] If nar-

> [I]f I am going to give you 15 years [of exclusivity] from the day your [biologic] product is approved, can I expect that your [patent] continuations that are still coming and—Ms. Rea, you are laughing, because you know how many of those sometimes are stacked up behind [already issued patents], is . . . part of the bargain that . . . *if you get [a patent] extraordinary separate from the normal patent period*, this Committee may have to consider whether or not that is a terminal disclaimer, so to speak, of some or all of your claims?

See Biologics and Biosimilars: Balancing Incentives for Innovation, Hearing Before Subcomm. on Courts and Competition Policy of H. Comm. on the Judiciary, 111th Cong. 235–36 (2009) [hereinafter *Biologics and Biosimilars Hearing*] (statement of representative Darrell Issa) (emphasis added). In other words, Representative Issa worried about biologic manufacturers using patent prosecution strategies to extend protection beyond the end of a lengthy exclusivity period. To illustrate the concern, a biologic product could be approved in 2015, with exclusivity running out in 2027 and patent protection lapsing in 2030, but patent prosecution strategies could result in additional patents being issued late in the product's lifecycle, stretching protection to 2045 and effectively giving the biologic 30 years of monopoly status. In response, all of the witnesses dismissed the need for legislation to address patent prosecution strategies. One witness, for example, asserted that the activity "should not be a problem" since the industry is marked by "incremental" improvements that "will have limited protections . . . such as manufacturing techniques" that can be "work[ed] around," which "essentially . . . solv[es the] problem for those later issuing patents." *Id.* at 236. In short, while there is little legislative history explaining how patent prosecution strategies such as submarine patents would affect the pathway for biosimilar approval, Representative Issa's exchange highlighted the concern.

351. 35 U.S.C. § 261 (2012) allows assignment, which can lead to shell licensing.

352. 42 U.S.C. § 262(l)(7) (2012) (allowing new patents to be raised); *id.* § 262(l)(8)(A)–(B) (providing for preliminary injunction).

353. 35 U.S.C. § 271(e)(6)(C); *see generally* Carver et al., *supra* note 119, at 760–61, 783, 786, 802–03 (discussing legislative history). In *Amgen v. Apotex*, the Federal Circuit stated, in dicta, that "[i]f a patent that the reference product sponsor should have included on its (3)(A) list or its (7) supplement 'was not timely included' then the owner of that patent may not sue for infringement under 35 U.S.C. § 271 with respect to the biological product at issue." 827 F.3d 1052, 1058 (Fed. Cir. 2016).

One view disputes the Federal Circuit's characterization of the BPCIA, suggesting that a textual reading of section 271(e)(6)(C)—referred to as the "list it or lose it" provision because it prevents a biologic from bringing infringement claims on patents not included in the initial exchange of lists nor within 30 days of a newly issued or licensed patent—only prevents a biologic from asserting patents under section 271(e)(2)(C) (the BPCIA infringement provision allowing suit before the follow-on has entered) rather than general infringement claims under section 271(a)–(c). Brian Coggio & Ron Voggel, *Can Reference Sponsor Forfeit Right To Sue Under BPCIA?*, LAW360 (July 25, 2016, 12:51 AM), https://www.law360.com/articles/820197. While section 271(e)(6)'s use of the language "this section" offers support for the view, the legislative history points to a broader reading of the list-it-or-lose-it provision. *See Biologics and Biosimilars Hearing*, *supra* note 350, at 69 (statement of Mr. Kushan on behalf of Biotechnology Industry Organization) (provision "single[s] out biotechnology patents only for limitations that undoubtedly alter the capacity of these patents to prevent unauthorized use of the protected technology"); *see also id.* at 207 (statement of Teresa Rea on behalf of American Intellectual Property Law Association) (list-it-or-lose-it provision is strict because it attaches to patent itself, rather than enforcement rights of biologic or licensor).

We take no position on this statutory debate but emphasize that future courts dealing with late-filed patent assertions will need to address whether the "list it or lose it" provision, section 271(e)(6)(C), results in the loss of only section 271(e)(2) claims or all infringement claims for not including a biologic patent that "should have been included."

rowly read to encompass only those holding *title* to the patent at the time of the patent dance (rather than those with overall *control* of the patent's assertion, as would a biologic over a shell-licensed patent), the manufacturer could exploit a loophole to ensnare the biosimilar maker.

This regulatory evasion contravenes the intent of the BPCIA and raises significant competitive concerns. Phase-One litigation is designed to provide significant control to the biosimilar applicant over patent resolution.[354] For that reason, the biosimilar maker naturally will seek to gain certainty concerning a manufacturer's strongest patents.[355] The structure of the BPCIA itself makes this clear by granting a full eight years to resolve Phase-One litigation, with the biosimilar incentivized to determine the potential for infringement liability early in the process.[356] If a manufacturer is able to conceal relevant patents until years after Phase-One litigation is completed, a biosimilar applicant is exposed to a higher liability concern than it expected when agreeing on the patents to litigate during the patent dance. That raises the potential for delayed entry and an evasion of the BPCIA.[357]

b. Assessment

The use of submarine patents and shell companies exclusively licensing patents raises not only concern but also the question of whether antitrust law can address this conduct. We believe it can.

In settings outside the BPCIA, antitrust law generally does not punish the filing and prosecution of patents. But just as antitrust must take account of the regulatory regime when the Hatch-Waxman Act is not working as anticipated because of pay-for-delay settlements, evergreening, and fraudulent patent listing, so too must it do so when the BPCIA is undermined through the use of patent prosecution tools to obtain submarine patents and exploit shell companies. *Trinko*'s direction that antitrust analysis should be "attuned to the particular structure and circumstances of the industry at issue"[358] and take "careful ac-

354. Amgen Inc. v. Apotex Inc., 827 F.3d 1052, 1062 n.3 (Fed. Cir. 2016) (explaining that "applicant control" over Phase-One patent litigation "is part of the design").

355. *See Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 110th Cong. 119 (2007) (statement of Bruce Downey, Chairman of Generic Pharmaceutical Association and CEO of Barr Pharmaceuticals) ("[B]iological patent system should provide mechanism for litigating only those patent disputes that the generic company believes would delay its launch.").

356. *See infra* note 384 and accompanying text. The legislative history reveals that stakeholders on both sides of the competitive ledger identified the benefits of resolving patent uncertainty before follow-on approval and the expiration of exclusivity. *See Biologics and Biosimilars Hearing*, *supra* note 350, at 35 (biosimilar maker Momenta explained that, because parties anticipate biologic patent litigation lasting four years, it is "essential" for patent resolution provisions "to assure and provide for the artificial act of infringement to occur at least four years prior to expiration of data exclusivity"); *see also id.* at 77 (testimony of Jeffrey P. Kushan, on behalf of Biotechnology Industry Organization) ("Nearly all stakeholders in the biosimilars debate support inclusion of procedures to identify and resolve patent issues before a biosimilar is approved and placed on the market.").

357. *See* Minniti, *Biosimilar Litigation*, *supra* note 332, at 5 ¶ 2 (discussing early trends in interpretation of BPCIA's patent resolution and concluding that lower courts are rejecting plain-text arguments in favor of channeling disputes to patent dance).

358. Verizon Commc'ns, Inc. v. Law Offices of Curtis V. Trinko, LLP, 540 U.S. 398, 411 (2004).

count" of "the pervasive federal and state regulation characteristic of the industry"[359] is at least as relevant here as it is in the small-molecule setting.

As the *Enbrel* example showed,[360] submarine licensing already presents a threat. Coherus BioSciences, a leading biosimilar manufacturer, noted in its 2015 10-K report that "[s]o called 'submarine' patents may be granted to our competitors that may significantly alter our launch timing expectations, reduce our protected market size, cause us to modify our product or process, or block us from the market altogether."[361]

In contrast, shell licensing in this setting has not yet been publicly revealed. But if history serves as a guide, and given the absence of a public Orange Book, such behavior threatens a new form of regulatory evasion. One example of the concerns of shell licensing has been raised in the context of patent assertion entities ("PAEs," often called "patent trolls"). A recent FTC report found that some PAEs employed a model consisting of multiple affiliates, which allowed them to obscure the identity of "related LLCs when negotiating with a prospective licensee" as well as "the individuals and entities that share in the [PAE's] licensing proceeds."[362] In fact, affiliates often cannot be linked to PAEs through their names, which results in defendants not knowing how to "identify the beneficial party or true party-in-interest" or even if they "already ha[ve] a license" through earlier deals with related entities.[363]

In comparing biologics to small-molecule drugs, there are differences between fraudulent Orange Book listings and the type of conduct we foresee under BPCIA litigation. For starters, the immediate harm of abusing Phase-One BPCIA litigation would appear to be less than in the small-molecule context. Under the Hatch-Waxman Act (especially before the 2003 amendments), the concern was that late or fraudulent patent listings in the Orange Book could automatically lead to a 30-month stay of generic approval.[364] In other words, while the FDA was performing the ministerial task of publishing patents in the Orange Book, brands' conduct compelled the agency to take an action that would delay generic entry. No similar provision appears in the BPCIA, which, instead, offers an 8-year window for the resolution of Phase-One litigation.[365]

Yet when it comes to Phase-Two litigation, the window for resolution is smaller and the potential for delay is higher. Phase-Two litigation begins with the biosimilar's notice of commercial marketing, which will take place only 180 days later. As a result, raising a hidden patent (and obtaining an injunction) months before a biosimilar is expected to enter the market could delay entry. This is particularly true if biosimilar competitors launch at risk and are already on the market driving down costs. And while the biologic likely will argue that any delay is the result of a court finding a likelihood of success in proving infringement, the biosimilar was never afforded an opportunity to con-

359. *Id.* (quoting United States v. Citizens & S. Nat'l Bank, 422 U.S. 86, 91 (1975)).
360. *See supra* notes 337–40 and accompanying text.
361. COHERUS BIOSCIENCES, ANNUAL REPORT (FORM 10-K), at 50 (Feb. 29, 2016).
362. FTC, PATENT ASSERTION ENTITY ACTIVITY 52 (2016).
363. *Id.* at 52–53.
364. *See supra* notes 299–314 and accompanying text.
365. *See infra* note 384 and accompanying text.

test that patent during Phase-One litigation, when final rulings (as opposed to tentative preliminary injunction determinations) on infringement could have been completed.

While the BPCIA was designed to offer biosimilar applicants the chance to raise in Phase One any patents for which they had infringement concerns, this educated risk assessment does not apply to submarine or shell-licensed patents. In these cases, the biosimilar applicant never has the opportunity to compare its product to the claims during Phase One. As a result, the biosimilar maker could face significant liability for patents it never had the chance to challenge in the stage of the process at which such challenges were anticipated. Conducting an infringement analysis is costly and time-consuming, which is why eight years of exclusivity are allocated to the resolution of these issues.[366] This is particularly true for submarine patents filed before June 7, 1995 (the last date current submarine applications could have been filed[367]) that claim subject matter from the early 1990s when fundamental biotechnology was still being developed. This could have significant anticompetitive effects because, in the years since then, products have incorporated that older technology, potentially infringing the basic subject matter claimed in the submarine patent and causing grave uncertainty.[368]

If future courts confront late-asserted patents in Phase Two, they should consider several points. First, before any patent is asserted in Phase Two, the BPCIA already would have required the parties to enter into "good faith negotiations" to agree on patents to be litigated during Phase One. Simply put, if a manufacturer knows it is *currently* prosecuting submarine patents it plans to assert in Phase Two, or is aware that other patents will become available through shell licensing, then the "good faith negotiation" mandate will have been violated. Despite this concern, however, the BPCIA framework does not empower the FDA to remedy bad-faith negotiation. Unlike the Hatch-Waxman Act, pursuant to which the FDA plays at least *some* ministerial role in publishing Orange Book patents,[369] the FDA is *wholly without power* to address biologic patent disputes. In addition, even though Congress considered requiring the FDA to appoint a special master to review a biologic's initial list to ensure that the patents were included in good faith, the BPCIA ultimately did not con-

366. *Id.*

367. *See* 35 U.S.C. § 154(a)(2)–(3) (codifying Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809); Ariad Pharm., Inc. v. Eli Lilly & Co., 529 F. Supp. 2d 106, 136 n.46 (D. Mass. 2007) ("Prior to June 1995, patent owners who experienced a long examination period before the patent issued in effect obtained an extension of the term of their patent grant."), *rev'd in part on other grounds*, 560 F.3d 1366 (Fed. Cir. 2009).

368. *See e.g.*, Gene Quinn, *Submarine Patents Alive and Well: TiVo Patents DVR Scheduling*, IPWATCHDOG (Feb. 19, 2010), http://www.ipwatchdog.com/2010/02/19/submarine-patents-alive-and-well-tivo-patents-dvr-scheduling/id=9168/ (discussing submarine patent issued to TiVo in 2010, from application filed in 1999, related to data storage management and scheduling that "will apply to pretty much any and all DVRs currently on the market").

369. *See* Kurt R. Karst, *A New Orange Book First: FDA Unilaterally Changes a Patent Use Code*, FDALAWBLOG (Nov. 20, 2016), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2016/11/a-new-orange-book-first-fda-unilaterally-changes-a-patent-use-code.html (noting that FDA has taken action regarding patents in Orange Book, particularly in response to regulations that went into effect in December 2016).

tain the provision, putting the burden and trust on the parties to abide by good-faith dealing.[370]

Applying *Trinko*'s direction to consider the regulatory framework underscores the FDA's inability to address anticompetitive harm. In *Trinko*, the Court explained that phone companies providing local service were required to "be on good behavior" and not to discriminate in providing access to certain facilities before they could enter the long-distance market.[371] The *Trinko* Court specifically recognized that where "there is nothing built into the regulatory scheme which performs the antitrust function, the benefits of antitrust are worth its sometimes considerable disadvantages."[372]

The BPCIA framework offers a textbook example of a regime in which the regulatory agency is without power to remedy anticompetitive conduct. The FDA itself has recognized its limited power, conceding that the statute "generally does not describe any FDA involvement in monitoring or enforcing the information exchange by creating a certification process or otherwise."[373] The "only express role" for the agency in relation to patent disputes appears in a separate provision, which "directs a biosimilar applicant to provide the Agency with notice and a copy of certain patent infringement complaints" that the FDA must publish in the Federal Register.[374]

In fact, the "lack of an explicit certification requirement" offers a distinct contrast to the Hatch-Waxman Act, which mandates that brands and generics make various certifications.[375] For that reason, the agency has conceded that, "[v]iewed against the explicit requirements" of the Hatch-Waxman Act, any contention that the FDA "'should' require a certification for biosimilar applications implicitly acknowledges that imposing such a requirement is a matter of regulatory discretion and not compelled" by the statute.[376]

When submarine or shell-licensed patents of which a biologics manufacturer is fully aware during the patent dance are asserted late in the BPCIA litigation process, plaintiffs could claim monopolization under Section 2 of the Sherman Act.[377] To be liable for monopolization, a company must have monopoly power and engage in exclusionary conduct. The first element is monopoly power, which has been defined as "the power to control prices or exclude competition."[378] The Supreme Court has held that a market can consist of a single product,[379] and numerous courts have found that a single drug can constitute its own market, which has naturally led to the conclusion of monop-

370. Carver et al., *supra* note 119, at 761.

371. Verizon Commc'ns, Inc. v. Law Offices of Curtis V. Trinko, LLP, 540 U.S. 398, 412 (2004); *see supra* notes 321–22 and accompanying text.

372. *Trinko*, 540 U.S. at 412.

373. Letter from Janet Woodcock, M.D., Dir., Ctr. for Drug Eval. & Research, to Jeffrey Kushan, Attorney, Sidley Austin (Mar. 25, 2015), https://www.regulations.gov/document?D=FDA-2014-P-1771-0004 (FDA denial letter).

374. *Id.* at 3 n.13 (citing § 351(1)(6)(C)(ii)).

375. *Id.* at 3–4.

376. *Id.* at 4.

377. 15 U.S.C. § 2 (2012).

378. United States v. E.I. duPont de Nemours & Co., 351 U.S. 377, 391 (1956).

379. *E.g.*, Eastman Kodak Co. v. Image Technical Servs., Inc., 504 U.S. 451, 481–82 (1992).

oly power.[380] Where potential purchasers have no alternative to using a particular product, as will typically be the case with expensive, complex, and pathbreaking biologics,[381] monopoly power is likely.

The case law on exclusionary conduct is less clear. Courts often distinguish between the "willful acquisition or maintenance of [monopoly] power" and "growth or development as a consequence of a superior product, business acumen, or historic accident."[382] To be sure, courts have not yet found that the prosecution of submarine patents, standing alone, constitutes exclusionary conduct.[383]

But the use of submarine patents and shell-licensed patents would appear to be anticompetitive conduct that in the context of the BPCIA—with its intricately choreographed moves and countermoves between the parties, lack of certification requirement, and windfall from late-filed patents—makes no sense other than by harming rivals. In particular, the two forms of conduct directly contravene the structure of Phase-One litigation, which is designed to resolve infringement issues during the eight years before manufacturers' exclusivity ends.[384] If biologic patents could be shielded for this extended period of time in which resolution is supposed to occur and the need for injunction determined, a core purpose of the BPCIA would be undermined. In fact, the market expectations of biosimilar entry after Phase-One resolution would be thwarted and future biosimilar applicants would question the certainty offered by Phase-One litigation. Instead, much like the concern leveled against PAEs, biosimilar makers would be relegated to a state of uncertainty during which patents would be unearthed after Phase One's period for patent resolution has ended. Such uncertainty would hinder competition in an already high-risk market with significant barriers to entry. And it would contravene the statute.

In short, the BPCIA allows the parties to determine which patents will be litigated. But if the biologic manufacturer games the system, entry could be delayed and consumers could be harmed. The likelihood that such anticompeti-

380. *E.g.*, *In re* Aggrenox Antitrust Litig., 94 F. Supp. 3d 224, 247 (D. Conn. 2015) ("If [it] were not the case" that the brand was "able to charge supracompetitive prices," it "is not clear why [it] would have sued to prevent [generic] entry . . . ."); *In re* Nexium Antitrust Litig., 968 F. Supp. 2d 367, 388 (D. Mass. 2013) (rejecting defendants' claim that "other drugs may be used to treat heartburn"); *In re* Terazosin Hydrochloride Antitrust Litig., 352 F. Supp. 2d 1279, 1319 n.40 (S.D. Fla. 2005) (accepting market limited to brand and generic terazosin hydrochloride); *In re* Cardizem CD Antitrust Litig., 105 F. Supp. 2d 618, 680–81 (E.D. Mich. 2000) (holding that brand and generic versions of heart medication with chemical compound diltiazem hydrochloride constitute single market), *aff'd,* 332 F.3d 896 (6th Cir. 2003). *But see*, *e.g.*, Meijer, Inc. v. Warner Chilcott Holdings Co., 245 F.R.D. 26, 32–33 (D.D.C. 2007) (ordering discovery on oral contraceptives beyond brand and related generic version); *In re* Remeron Direct Purchaser Antitrust Litig., 367 F. Supp. 2d 675, 683 (D.N.J. 2005) (rejecting market definition limited to brand and generic versions because "[g]enerics normally enter the market with prices significantly lower than that of the first brand name manufacturers").

381. *See supra* Section II.B.

382. United States v. Grinnell Corp., 384 U.S. 563, 570–71 (1966).

383. *E.g.,* Inline Packaging, LLC v. Graphic Packaging Int'l, Inc., 164 F. Supp. 3d 1117, 1135 (D. Minn. 2016).

384. *See* 42 U.S.C. § 262(k)(7)(B) (2012); *see also* Lietzan, *supra* note 80, at 55 ("If a biosimilar application is submitted immediately after the four-year submission bar has ended, the parties should have more than seven years to resolve the first phase of litigation, and it should be possible to reach a final court decision on the patents included in that first phase.").

tive harms could arise from Phase-Two litigation calls for close antitrust scrutiny.

D. REMS

One particular example of regulatory abuse that has received attention in recent years involves Risk Evaluation and Mitigation Strategies ("REMS").[385] Designed to allow drugs with safety concerns to reach the market, brand and biologic manufacturers have used REMS to delay entry by refusing to share samples required by generic and biosimilar makers.

In 2007, Congress enacted the Food and Drug Administration Amendments Act ("FDAAA").[386] Section 505–1(a)(1) of the Act authorizes the FDA to require sponsors of drug applications (including brands, generics, and biologic manufacturers)[387] to submit a proposed REMS if the agency determines that it is needed to ensure that a drug's benefits outweigh its risks.[388] The FDA has defined REMS as "required risk management plans that use risk minimization strategies beyond professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks."[389] Examples of REMS requirements include education addressing the risk of serious infection, certification of healthcare professionals targeting severe allergic reactions, the monitoring of liver damage, and negative pregnancy tests to address severe birth defects.[390]

More restrictive REMS programs have "Elements To Assure Safe Use (ETASU)," which can limit a drug's distribution.[391] Since their enactment in 2007, REMS programs—in particular, those with ETASU requirements—have become an increasingly prevalent part of the FDA approval process. 40 percent of new drugs have REMS programs,[392] and there are currently 77 approved REMS programs, with 42 of these requiring ETASU measures.[393] Of these 77 REMS, 17 target biologics, with 9 employing ETASU restrictions.[394] Despite their increasing frequency, a report from the U.S. Department of Health and Human Services's Office of Inspector General questioned "the overall effec-

385. 21 U.S.C. § 355–1(a)(1) (2012).

386. FDA, *Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)*, at 3 (2014).

387. *Id.* at 9.

388. 21 U.S.C. § 355–1(a)(1) (2012).

389. FDA, A BRIEF OVERVIEW OF RISK EVALUATION & MITIGATION STRATEGIES (REMS), at 2, [hereinafter FDA REMS OVERVIEW], http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf (last visited Nov. 2, 2017).

390. *Id.* at 3, 13.

391. *Id.* at 7.

392. Darren S. Tucker, Gregory F. Wells & Margaret E. Sheer, *REMS: The Next Pharmaceutical Enforcement Priority?*, 28 ANTITRUST 74, 74 (2014).

393. FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS),* http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17 (last visited Sept. 2, 2017).

394. *Id.* The nine biologics are Aransep, Epogen/Procrit, Lemtrada, Myalept, Natpara, Soliris, Tysabri, Xiaflex, and Zinbryta.

tiveness of the REMS program," with just 7 of 49 REMS meeting all their goals.[395]

A central concern is that biologic manufacturers can exploit REMS to prevent biosimilars from entering the market. Generics and biosimilars must have access to samples[396] to reach the market.[397] Typically, these parties can acquire samples from distributors or wholesalers.[398] But when REMS programs foreclose this route, brands and biologics offer the only option.[399] And when there is no access to samples, generics and biosimilars must replicate the original trials. Such conduct contravenes the FDAAA, which makes clear that ETASU measures cannot be used to "block or delay" follow-on applications.[400] And it undercuts the Hatch-Waxman Act and BPCIA, which are based on follow-on competition.

1. Small Molecules

Courts have recently analyzed the use of REMS to block or delay generics. This is a nascent issue, analyzed in only seven cases to date, none past the motion-to-dismiss stage. Two primary themes have emerged in the case law relating to sample denials.

The first theme is that the FDA lacks the power to compel a brand to provide samples. For that reason, the situation differs from that in *Trinko*, where the Court rejected a role for antitrust law because of a regulatory regime by which the Federal Communications Commission ("FCC") had remedial authority.[401] In noting that the Supreme Court's refusal-to-deal decisions were "fact-specific" and "industry-specific,"[402] the court in *Actelion v. Apotex* observed that "[t]he FDA is not the FCC" but is "a different environment," which made "clear" that the agency "d[id] not have the regulatory power to compel samples" and that "there [was] no other potential remedy to a defendant suffering anticompetitive conduct in that regulatory scheme."[403] As a result, while the court was "mindful of what Justice Scalia said" in *Trinko*[404] that "it's not the role of this Court or any Court to impose its own sense of competition or

395. OFFICE OF INSPECTOR GEN., DEP'T HEALTH & HUMAN SERVS., FDA LACKS COMPREHENSIVE DATA TO DETERMINE WHETHER RISK EVALUATION AND MITIGATION STRATEGIES IMPROVE DRUG SAFETY 16 (2013), https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf.

396. Ctr. for Drug Evaluation & Research (CDER), *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD Guidance for Industry* 4 (Dec. 2014), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm425662.pdf.

397. *The CREATES Act: Ending Regulatory Abuse, Protecting Consumers, and Ensuring Drug Price Competition Before the S. Judiciary Subcomm. on Antitrust, Competition, Policy and Consumer Rights*, 114th Cong. 2 (2016) [hereinafter *CREATES Act Hearing*] (statement of Beth Zelnick Kaufman).

398. Lauren Battaglia, *Risky Conduct with Risk Mitigation Strategies? The Potential Antitrust Issues Associated with REMS*, ANTITRUST HEALTH CARE CHRON. 28 (2013).

399. *Id.*

400. 21 U.S.C. § 355–1(f)(8) (2012).

401. Verizon Commc'ns, Inc. v. Law Offices of Curtis V. Trinko, LLP, 540 U.S. 398, 411–12 (2004).

402. Transcript of Motions Hearing at 115, Actelion Pharm. Ltd. v. Apotex, Inc., (No. 12-5743), 2013 WL 5524078 (D.N.J. Oct. 17, 2013) [hereinafter *Actelion v. Apotex Transcript*].

403. *Id.* at 115–16.

404. *Trinko*, 540 U.S. at 411.

fairness or to become a super-regulatory agency,"[405] that case does not "repeal Section 2,"[406] which allowed the generics to allege "a profit motive which did not exist in *Trinko*."[407]

The second theme is that the facts underlying a REMS refusal to deal need not mirror those in Supreme Court cases, in particular reflecting a previous course of dealing.[408] The *Mylan v. Celgene* court found that Third Circuit cases had found prior dealing to be "relevant but not dispositive" in determining whether a duty to deal applies.[409] In particular, the court noted that *Trinko* considered facts like selling at retail and a prior course of dealing "not for their independent significance, but rather for what they *suggest*: [a] willingness to engage in irrational, anticompetitive conduct."[410] The court denied a motion to dismiss because the defendant failed to plead a "legitimate business reason" for its behavior.[411]

To similar effect, the court in *In re Thalomid and Revlimid Antitrust Litigation* found that the termination of dealing in *Aspen Skiing v. Aspen Highlands Skiing*[412] was "used as circumstantial evidence" of the defendants' "anticompetitive motivation" and "lack of legitimate business justifications"[413] and that there was a "plausible inference" that the brand's reliance on its distribution programs was "pretextual" since it "continued to refuse to deal" even after the generics provided FDA letters indicating that "the agency would not take action if [the brand] provided samples."[414]

405. *Actelion v. Apotex* transcript, *supra* note 402, at 116.

406. *Id.*

407. *Id.* at 115.

408. *Trinko*, 540 U.S. at 410, 412–13 (explaining that Telecommunications Act sought to break up local monopolies by requiring incumbent carriers to share networks with competitors and that presence of regime that included penalties and reporting requirements significantly reduced "the additional benefit to competition provided by antitrust enforcement"); Aspen Skiing Co. v. Aspen Highlands Skiing Corp., 472 U.S. 585, 605–11 (1985) (finding that owner of three downhill skiing facilities failed to offer justification for withdrawing from joint ticketing arrangement with owner of only other facility in area and was liable for anticompetitive conduct for forgoing ticket sales and sacrificing profits to harm smaller competitor); Otter Tail Power Co. v. United States, 410 U.S. 366, 377–82 (1973) (holding that company in business of providing electric power transmission could not "refuse[] to provide the same service to certain other customers," as its "refusals to sell . . . were solely to prevent municipal power systems from eroding its monopolistic position").

409. Transcript of Oral Opinion at 12–13, Mylan Pharmaceuticals Inc. v. Celgene Corp., No. 2:14-cv-02094-ES-MAH, 2015 WL 409655 (2014).

410. *Id.* at 9 (emphasis in original).

411. *Id.* at 17–18; *see* Natco v. Gilead Sciences, Civ. No. 14-3247 (DWF/JSM), 2015 WL 5718398 (D. Minn. Sept. 29, 2015) (denying liability on the ground that the generic could have received the drug through a REMS-certified physician).

412. 472 U.S. 585 (1985).

413. *In re* Thalomid and Revlimid Antitrust Litig., No. 14-6997, 2015 WL 9589217, at *15 (D.N.J. Oct. 29, 2015).

414. *Id.* at 5, 15.

2. Biologics

The issue of sample denials has already arisen in the biologics setting. Of the 77 currently approved REMS programs, 17 cover biologics.[415] According to one survey of follow-on makers, biosimilar manufacturers have reported restricted access to biologic samples.[416]

a. Likelihood

Because the characteristics of biologics increase the likelihood of safety concerns, REMS programs are as likely to apply to biologics as they are to small molecules. As explained in detail above,[417] biologics are more complex than small molecules, undergo changes during the product's maturation, and do not allow the analysis of protein structure, which make it more difficult to predict how they will operate.[418] As a result, the FDA will (at a minimum) be as likely to impose REMS programs on biologics as on small-molecule drugs.

b. Assessment

A biologic manufacturer's denial of a sample needed by a biosimilar maker threatens antitrust harms as significant as those presented in the small-molecule setting. Indeed, since biosimilars lack "access to originator companies' proprietary data, . . . [b]iosimilar product development begins with an intensive reverse engineering project,"[419] which makes a sample critical.

From an antitrust vantage point, this is not just a naked refusal to deal in a vacuum. It is a refusal in a regulatory setting in which biosimilar entry was designed to lower prices[420] and in which (if history serves as a guide) Congress is likely to extend the FDAAA's prohibition on "block[ing] or delay[ing]" follow-on approval to biologics.[421] The Supreme Court in *Trinko* explained that

415. *See supra* notes 393–94 and accompanying text.

416. Alex Brill, MATRIX GLOBAL ADVISORS, *Lost Prescription Drug Savings From Use of REMS Programs to Delay Generic Market Entry*, at 6 (July 2014), http://www.gphaonline.org/media/cms/REMS_Studyfinal_July2014.pdf.

417. *See supra* notes 32–52 and accompanying text.

418. *See supra* notes 32–52 and accompanying text; *see, e.g.*, *Biologics, Inc. Selected by AstraZeneca as Exclusive Channel Partner for Vandetanib*, BIOLOGICS, INC. (Apr. 25, 2011), https://www.biologicsinc.com/843/biologics-inc-selected-by-astrazeneca-as-exclusive-channel-partner-for-vandetanib-3/ (explaining that REMS required because of "risks of [racing heart condition] QT prolongation, [abnormal heart rhythm] Torsades de pointes, and sudden death").

419. NIAZI, *supra* note 21, at 74.

420. *See supra* Part II.

421. *See supra* note 400 and accompanying text. As it currently stands, the provision banning the use of REMS with ETASU "to block or delay approval," 21 U.S.C. § 355–1(f)(8) (2012), does not explicitly refer to biosimilar applications under 42 U.S.C. § 262(k), instead addressing only small-molecule generic and 505(b)(2) applications. But an expansion of section 355–1(f)(8) to cover biosimilar applications would be consistent with how statutes have evolved in similar contexts. For example, when Congress enacted the FDAAA in 2007, it mandated that the FDA resolve citizen petitions asking the agency not to approve a pending generic application (generally filed by brand companies and referred to as "505(q) petitions") within 180 days. Although this originally applied only to generic applications referencing small-molecule brands, in 2012 Congress passed the Food and Drug Administration Safety and Innovation Act ("FDASIA") which, among other things, expanded the FDA's mandate to include biosimilar applications. Pub. L. 112–144, 126 Stat. 993 (2012). Along those same lines, we anticipate that Congress will (and should) expand section 355–1(f)(8) to include a prohi-

courts applying antitrust law must take "careful account" of "the pervasive federal and state regulation characteristic of the industry"[422] and that the analysis must "recognize and reflect the distinctive economic and legal setting of the regulated industry to which it applies."[423]

In the setting here, biosimilar manufacturers need access to a sample to reach the market, but the regime is not working as intended, and the FDA does not have the power to remedy the concern. Despite the statute's prohibition on blocking or delaying competition, more than 100 firms have complained that they have not been able to access samples they need to reach the market.[424] Senators have lamented that the refusal to share samples is a "simple delay tactic [that] uses regulatory safeguards as a weapon to block competition"[425] and that brand and biologic manufacturers have "misus[ed]" REMS "in violation of FDA regulations and the Hatch-Waxman Act."[426]

Not only is the regime not working as intended, but the FDA is unable to fix the problem. A Senate committee concluded that the agency "has attempted to stymie [brands'] obstruction" by providing letters indicating that "they . . . see no safety risk," but its actions "have been largely ineffective."[427] It thus is not a surprise that the FDA has conceded that "issues related to ensuring that marketplace actions are fair and do not block competition would be best addressed by the FTC, which is the federal entity most expert in investigation and addressing anticompetitive business practices."[428]

Because the FDA has no power to compel a sale, the regulatory regime is not able to address competitive industry harms, ensuring an opportunity for antitrust enforcement. And antitrust can play a uniquely effective role in analyzing behavior so extreme that it fails even the conservative, defendant-friendly, no-economic-sense test.[429] Absent a showing, not revealed to date, of below-market-rate offers, the denial of samples makes no economic sense other than by harming follow-on competition.

No case has yet arisen challenging biologics' denial of samples to biosimilars. But we believe the application of the no-economic-sense test in the context of the regulatory regime supports monopolization claims for sample

bition on using REMS with ETASU "to block or delay approval" of biosimilar applications under 42 U.S.C. § 262(k).

422. Verizon Commc'ns. Inc. v. Law Offices of Curtis V. Trinko, LLP, 540 U.S. 398, 411 (2004) (quoting United States v. S. Nat'l Bank, 422 U.S. 86, 91 (1975)).

423. *Id.* (quoting Town of Concord, Mass. v. Bos. Edison Co. 915 F.2d 17, 22 (1st Cir. 1990)).

424. Press Release, U.S. Senator Patrick Leahy of Vermont, The Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act of 2016 (Apr. 27, 2017), https://www.leahy.senate.gov/imo/media/doc/CREATES%20Act%20-%20Press%20Background%20Materials%20updated%204.24.17.pdf.

425. *Id.* (statement of Senator Patrick Leahy).

426. *CREATES Act Hearing*, *supra* note 397 (statement of Senator Chuck Grassley).

427. *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System S. Special Comm. on Aging*, 114TH CONG. 115 (2016).

428. Partial Petition Approval & Denial at 7, No. FDA-2009-P-0266-0006 (Aug. 7, 2013). *Cf.* Grant in Part and Denial in Part, No. FDA-2013-P-0572 (Oct. 7, 2013) (FDA response to citizen petition explains that "[t]o the extent that . . . there may be antitrust issues associated with establishing single, shared systems," the party should "consult with the FTC").

429. *See supra* notes 278–89 and accompanying text.

denials.[430] Most fundamentally, a biologic's refusal to provide a REMS sample constitutes exclusionary conduct since it makes no economic sense other than by harming biosimilars. Although specific offers have not yet been revealed in the biologics context, generics in the small-molecule setting have been willing to pay a high price for samples, with one even stating that it paid "ridiculous amounts of money" for "a commercially immaterial quantity of the drug."[431] And given the significantly higher price of biologic drugs,[432] the profit biologics could receive from selling samples would be even higher than in the small-molecule setting.[433]

A willingness to buy samples at a profitable market rate reveals denials falling comfortably within the range in which courts have found liability because of a refusal to accept a retail price. For example, in *Aspen Skiing*, the defendant "was willing to sacrifice short-run benefits and consumer goodwill in exchange for a perceived long-run impact on its smaller rival,"[434] and in *Otter Tail Power Co. v. United States*,[435] the defendant was already providing electric-power transmission but refused to provide it to competitors "to prevent municipal power systems from eroding its monopolistic position."[436]

Drug samples also are far closer to the services available to the public under *Aspen Skiing* and *Otter Tail* than the "brand new" type of service in *Trinko* that "exist[ed] only deep within the bowels" of Verizon.[437] For REMS programs that the FDA requires after the drug is already on the market, by definition the product is available. Even when a sample is requested before a drug is approved, the biologic maker is in the business of producing drugs. And once it has manufactured the product, providing a sample involves no additional effort. It is not as if the manufacturer needs to embark on a separate process of creating a new product just to provide a sample to the biosimilar maker.

430. In the REMS cases litigated to date, proving monopoly power has not been a hurdle. One reason is the procedural setting, with courts crediting plaintiffs' allegations related to the factually intensive determination of monopoly power in the context of a motion to dismiss. *See In re* Suboxone Antitrust Litig., 64 F. Supp. 3d 665, 678–79 (E.D. Pa. 2014); Transcript of Oral Opinion at 9, Mylan Pharms. Inc. v. Celgene Corp., 2015 WL 409655 (2014) (No. 2:14-cv-02094-ES-MAH); Transcript of Motions Hearing at 117, Actelion Pharm. Ltd. v. Apotex, Inc., 2013 WL 5524078 (2013) (No. 1:12-cv-05743). But as the cases proceed to later stages, analysis could very well reveal monopoly power, reflecting the control that brands typically have over markets consisting of REMS drugs. The factors, for example, that the FDA evaluates in requiring REMS imply a cost-benefit analysis that considers whether other drugs treat the same disease. FDA REMS OVERVIEW, *supra* note 389, at 6; Christopher Megaw, *Reviving Essential Facilities to Prevent REMS Abuses*, 47 COLUM. J.L. SOC. PROBS. 103, 132 (2013). Where there is a less dangerous alternative on the market, the FDA would not be likely to approve a new, more dangerous product. Instead, the agency is more likely to approve a risky REMS product only where there is no safer, effective alternative on the market. In other words, the REMS product is likely to fill an unmet medical need, lack close substitutes, and reflect monopoly power.

431. *CREATES Act Hearing*, *supra* note 397 (statement of Beth Zelnick Kaufman at 2:11).

432. *See supra* Section II.C.

433. In the small-molecule context, this willingness to pay the market rate has been accompanied by brands' seemingly irrational responses. *See* Transcript of Oral Opinion, *supra* note 409, at 4–7. As of the date of this Article, and eight years after entering into an indemnification agreement, Mylan still has not provided requested samples.

434. *Aspen Skiing Co. v. Aspen Highlands Skiing*, 472 U.S. 585, 610–11 (1985).

435. 410 U.S. 366 (1973).

436. *Id.* at 378. In contrast, in *Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP*, 540 U.S. 398, 399 (2004), Verizon could only obtain a "cost-based rate of compensation" under the relevant statute.

437. *Trinko*, 540 U.S. at 410.

The ready availability of samples offers additional evidence that the refusal to provide them constitutes behavior that makes sense only by harming rivals.

In short, the denial of a sample threatens the entire regulatory scheme. Nor is the agency closest to the behavior, the FDA, interested in addressing these issues. For that reason, antitrust has a crucial role to play in addressing the denial of biologic samples.[438]

E. Citizen Petitions

Just as REMS-related conduct evades a legislative instruction, *citizen petitions* have been used to exploit the regulatory process. Citizen petitions are a means by which any "interested person" can request that the FDA "issue, amend, or revoke a regulation or order" or "take or refrain from taking any other form of administrative action."[439] In particular, they allow any party to raise safety or effectiveness concerns with drugs the FDA is considering for approval.[440] The petitions, with a foundation in the First Amendment[441] and the Administrative Procedure Act,[442] play an important role, in theory, in ensuring that drugs are safe and effective. In practice, however, brand firms have used petitions to delay generic approval, extending their monopolies at a potential cost of millions of dollars per day.[443] In many cases, petitions offer little incremental value but require considerable time, with the FDA forced to address the merits of every petition, many of which contain "detailed analysis and precise scientific documentation" and require review by "multiple disciplines" within the agency.[444] Just to give one example, a citizen petition played a crucial—albeit underappreciated—role in the 400% price increase of Mylan's EpiPen.[445]

438. For a rebuttal of justifications brands have offered based on the case law (that there is no duty to deal but there is a prior-course-of-dealing requirement) and business arguments based on concerns about safety and product liability, see Michael A. Carrier, *Sharing, Samples, and Generics: An Antitrust Framework*, 103 CORNELL L. REV. 1 (2017).

439. 21 C.F.R. §§ 10.25, 10.30 (2017).

440. *Id.*

441. U.S. CONST. amend. I.

442. 5 U.S.C. § 553(e) (2002) (requiring government agencies to provide public with right to petition for issuance, amendment, or repeal of rule).

443. For example, in a contested battle over the introduction of generic versions of depression-treating Seroquel, AstraZeneca argued for a temporary restraining order vacating the FDA's final approval of a generic because absent such relief, it would lose more than $2 billion in sales with "most, if not all, of this sales loss [occurring] literally within a day or two after final approval." AstraZeneca Pharm. LP v. FDA, No. 12-472, 2012 WL 1037457, at *2 n.2 (D.D.C. Mar. 28, 2012).

444. *The Generic Drug Maze: Speeding Access to Affordable, Life-Saving Drugs: Hearing Before the S. Spec. Comm. on Aging*, 109th Cong. 14 (2006) (statement of Gary Buehler, Director, Office of Generic Drugs, FDA).

445. Carrier & Minniti, *The Untold EpiPen Story*, *supra* note 167, at 64–66; *see* Anna Edney & Cynthia Koons, *Mylan Plans Generic EpiPen to Quell Outcry Over $600 Cost*, BLOOMBERG (Aug. 29, 2016, 5:26 AM), https://www.bloomberg.com/news/articles/2016-08-29/mylan-to-sell-generic-epipen-to-quell-outcry-over-600-cost; *see also* Ed Silverman, *How Mylan Tried to Keep Teva from Selling a Generic EpiPen*, STAT (Aug. 31, 2016), https://www.statnews.com/pharmalot/2016/08/31/mylan-teva-generic-epipen/ (commenting that Mylan petition asking FDA not to approve Teva's proposed generic relied on supplemental study that "had a lot of problems," as it "lacked a control group, did not study the actual generic but a prototype instead, used a small number of participants, failed to provide them with proper instructions for use, and told participants to watch a video rather than actually use the Teva device").

1. Small Molecules

In the small-molecule setting, some citizen petitions have focused on procedural issues.[446] But many others have made substantive requests for the FDA to refrain from approving a generic competitor. These brand petitions typically have sought to require the generic to perform additional testing before entering the market.[447] They also have questioned whether generics are bioequivalent—in other words, able to deliver the same amount of active ingredient with the same rate and extent of absorption into the body.[448] In short, brands have used the process as a last-ditch effort to prolong their monopoly power.[449]

Before 2007, citizen petitions requesting that the FDA refrain from approving a pending generic application resulted in the withholding of generic approval until the petition was resolved.[450] This tempted brand firms to file petitions for the purpose of delaying generic approval.[451]

In attempting to combat the potential for this abuse, Congress targeted a class of particularly concerning petitions: those asking the FDA not to approve a pending generic or hybrid (sometimes called "paper") application.[452] These are known as *505(q) citizen petitions*. Through the FDAAA,[453] Congress provided that the agency shall not delay approval of a pending ANDA or paper NDA as a result of a petition unless it found that the delay was necessary to protect public health.[454] To accomplish this mission, the FDA must resolve all 505(q) petitions within 150 days—a time frame that would not be extended "for any reason."[455] The amendment also granted the agency the power to summarily deny petitions that have a "primary purpose of delaying approval of

446. For example, generics have filed "discontinuation" petitions with the FDA to determine if approved drug products were taken off the market for safety and efficacy reasons. *E.g.*, Wiley Rein LLP Citizen Petition, No. FDA-2015-P-1752-0001 (May 14, 2015), https://www.regulations.gov/document?D=FDA-2015-P-1752-0001.

447. Michael A. Carrier & Carl J. Minniti, III, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305, 328 (2016) [hereinafter Carrier & Minniti, *Citizen Petitions*].

448. *Id.*

449. 153 CONG. REC. S11,937–38, 2007 WL 2746562 (daily ed. Sept. 21, 2007) (statement of Sen. Ted Kennedy) ("FDA has a commonsense policy to allow ordinary citizens or medical experts to submit petitions to the agency about drugs that it is considering approving," but even though "[t]his procedure should be used to protect public health . . . too often, it is subverted by those who seek only to delay the entry onto the market of generic drugs.").

450. *See Statement of Director of Office of Generic Drugs Gary Buehler before S. Special Comm. on Aging* 7–8 (July 20, 2006), https://www.aging.senate.gov/imo/media/doc/hr161gb.pdf ("Although it is not required that a citizen petition response be issued before approval of a related ANDA, it is important that FDA comprehensively assess the scientific issues prior to approval of the ANDA. It is very rare that petitions present new issues that CDER has not fully considered, but the Agency must nevertheless assure itself of that fact by reviewing the citizen petitions.").

451. *See* Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249, 283–85 (2012) (discussing case of Wellbutrin XL, in which brand firm's petition resulted in 133 additional days of monopoly and may have resulted in more than $600 million in additional sales).

452. This latter category refers to a 505(b)(2) application, which, like a new drug application, "contains full safety and effectiveness reports," but, like an ANDA, "allows at least some of the information required for NDA approval, such as safety and efficacy information on the active ingredient, to come from studies not conducted by or for the applicant." *What Is 505(b)(2)?*, CAMARGO, http://camargopharma.com/what-is-505b2/ (last visited Nov. 14, 2017).

453. 21 U.S.C. § 355(q) (2012).

454. *Id.* § 355(q)(1)(A)(ii).

455. *Id.* § 355(q)(1)(F).

an application" and that "do[] not on [their] face raise valid scientific or regulatory issues."[456] The FDA has never used this power.

In previous work, we conducted an empirical study of 505(q) citizen petitions filed with the FDA between 2011 and 2015.[457] We observed that brands filed 92% of these petitions[458] and that the agency denied 92% of them.[459] We highlighted three particularly concerning aspects of petitions. First are late-filed petitions. Almost 40% of petitions were filed within 6 months of the expiration of a patent or FDA exclusivity period.[460] We hypothesized that filing a petition so close to these events could indicate that the filer seeks to exploit the process to keep a competitor off the market, which was supported by only 2% of these petitions being granted.[461] We also found that the average length of a 505(q) petition has more than doubled in the past 5 years, with the FDA granting a mere 3% of petitions with lengths above the mean.[462]

Another recent occurrence is the FDA's resolution of a petition on the same day (or in the same month) it approves an ANDA. The concern in this case is that generic entry could be delayed because the FDA does not approve the ANDA until it resolves the petition. We found that the agency approved 23 ANDAs within one month of resolving a petition raising concerns about the ANDA.[463] Of these 23 ANDAs, 6 were approved on the same day the FDA resolved the petition.[464] And in every case in which same-day (or even same-month) resolution and generic approval occurred, the 505(q) petition was denied.[465] In short, brands have exploited citizen petitions to delay generic approval.[466]

2. Biologics

We believe that there will be more petitions filed in the biologic setting than in the small-molecule context. And given the increased complexity of petitions addressing biosimilars, we foresee a potential reduction in the frequency of sham petitions violating the antitrust laws.

a. Likelihood

In the small-molecule setting, brands have regularly raised issues relating to a generic's safety and efficacy. And while each petition raises scientific ar-

456. *Id.* § 355(q)(1)(E).
457. Carrier & Minniti, *Citizen Petitions*, *supra* note 447.
458. *Id.* at 331.
459. *Id.* at 333. In an earlier article, one of us found that the FDA denied 81% of citizen petitions filed between 2001 and 2010. Carrier & Wander, *supra* note 451, at 274.
460. Carrier & Minniti, *Citizen Petitions*, *supra* note 447, at 338–41.
461. *Id.* at 341.
462. *Id.* at 337.
463. *Id.* at 342.
464. *Id.*
465. *Id.*
466. For proposed solutions to abuse of the citizen-petition process, see Michael A. Carrier, *Five Actions to Stop Citizen Petition Abuse*, 118 COLUM. L. REV. ONLINE (forthcoming 2018), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3043541.

guments specific to the drug at issue, petitioners have often requested additional bioequivalence testing, essentially forcing the generic maker to provide additional testing (thereby incurring development costs) beyond what is normally required for generic approval. Given that biosimilars present even larger differences with biologics and that immunogenicity concerns raise the potential for adverse health effects, we predict that biologic manufacturers are likely to file even more citizen petitions than brands have in the small-molecule setting.

Recent experience with the approval of nonbiologic complex drugs ("NBCDs") under the Hatch-Waxman Act could present a template for future biosimilar petitions. NBCDs typically consist of structures that cannot be isolated, fully characterized, or analyzed, making them less complex than biologics but more complex than small molecules.[467] The most high-profile NBCD is Teva's formerly $3-billion-a-year therapy Copaxone,[468] which is an NBCD treatment used to reduce the frequency of relapses with multiple sclerosis.[469] In April 2016, the FDA issued draft guidance explaining how prospective generics could demonstrate the active pharmaceutical ingredient sameness necessary for approval under the Hatch-Waxman Act.[470] Before issuing that guidance, however, the FDA employed multiple working groups and considered outside research and numerous comments.[471] Of note, Copaxone's sponsor, Teva Pharmaceuticals, filed *eight* different citizen petitions.[472] As one commentator put it: "[i]t's not just that Teva . . . doesn't want the FDA to approve generics of its MS star, Copaxone," but that it "*really, really, really* does not want the FDA to approve them . . . ."[473] The complex scientific issues raised by Teva's

467. *See* Daan J. A. Crommelin et al., *Different Pharmaceutical Products Need Similar Terminology*, AAPS J., Jan. 2014, at 11, 11–14, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3889525/.

468. After generics began competing in 2015, annual U.S. revenues fell to $960 million. Carly Helfand, *Teva's Copaxone Finally Succumbs to Copycats, Putting a Drag on 2015 Sales*, FIERCEPHARMA (Feb. 11, 2016, 11:47 AM), http://www.fiercepharma.com/financials/teva-s-copaxone-finally-succumbs-to-copycats-putting-a-drag-on-2015-sales; Tracy Staton, *Copaxone, Teva*, FIERCEPHARMA, http://www.fiercepharma.com/special-report/copaxone-teva (last visited Nov. 13, 2017).

469. Huub Schellekens et al., *How to Regulate Nonbiological Complex Drugs (NBCD) and their Follow-on Versions: Points to Consider*, AAPS J., Jan. 2014, at 15, 18, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3889532/.

470. FDA, DRAFT GUIDANCE ON GLATIRAMER ACETATE INJECTION (2016), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495029.pdf.

471. *See* Daan J.A. Crommelin, *Challenges for Non-Biological Complex Drugs (NBCDs)* (May 16, 2014), https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM398889.pdf.

472. *See, e.g.*, Teva Neuroscience, Inc., Citizen Petition No. FDA-2015-P-1050-0001 (Mar. 31, 2015), https://www.regulations.gov/document?D=FDA-2015-P-1050-0001; Teva Neuroscience, Inc., Citizen Petition No. FDA-2014-P-0933-0001 (July 2, 2014), https://www.regulations.gov/document?D=FDA-2014-P-0933-0001; Teva Pharm., Citizen Petition No. FDA-2013-P-1641-0001 (Dec. 5, 2013), https://www.regulations.gov/document?D=FDA-2013-P-1641-0001; Teva Neuroscience, Inc., Citizen Petition No. FDA-2013-P-1128-0001 (Sept. 12, 2013), https://www.regulations.gov/document?D=FDA-2013-P-1128-0001; Teva Neuroscience, Inc., Citizen Petition No. FDA-2012-P-0555-0001 (June 4, 2012), https://www.regulations.gov/document?D=FDA-2012-P-0555-0001; Teva Neuroscience, Inc., Citizen Petition No. FDA-2010-P- 0642-0001 (Dec. 10, 2010), https://www.regulations.gov/document?D=FDA-2010-P-0642-0001; Teva Neuroscience, Inc., Citizen Petition No. FDA-2009-P-0555-0001 (Nov. 13, 2009), https://www.regulations.gov/document?D=FDA-2009-P-0555-0001; Teva Neuroscience, Inc., Citizen Petition No. FDA-2008-P-0529-0001 (Sept. 26, 2008), https://www.regulations.gov/document?D=FDA-2008-P-0529-0001.

473. Carly Helfand, *Teva Takes Another Swing at Generic Copaxone with New FDA Petition*, FIERCEPHARMA (Apr. 2, 2015, 11:01 AM), http://www.fiercepharma.com/sales-and-marketing/teva-takes-another-swing-at-generic-copaxone-new-fda-petition (emphasis added).

use of citizen petitions provides insight into potential future biosimilar petitioning.

In 2012, Congress expanded the scope of Section 505(q) to include petitions targeting biosimilar applications,[474] and on January 9, 2017, the FDA finalized the rule.[475] As of the date of this Article, no biologic manufacturer has filed a 505(q) petition against a pending application for biosimilar approval. Other petitions have targeted legal issues related to biosimilars rather than questions related to specific approvals.

As for the legal issues, petitions were filed in 2013 regarding labeling requirements for biosimilars.[476] To decrease confusion, Novartis requested that the FDA "require that a biosimilar[] be identified by the same international nonproprietary name ["INN"] as the reference product" sponsor.[477] As a second example, the Generic Pharmaceutical Association petitioned for an INN naming policy that applied equally to all biologics given the already high bar of similarity that needs to be shown for approval.[478]

In 2014, Amgen submitted a petition requesting that all biosimilar applicants be required to sign a certification that they would timely comply with the patent-exchange provisions.[479] The FDA denied the petition, reasoning that the BPCIA differed from the Hatch-Waxman Act by not including mandatory certification language.[480] Instead, the agency explained that the statute was silent on the issue and, thus, declined to impose such an obligation on the biosimilar applicant.[481]

Four petitions filed in 2015 and 2016 concerned the labeling of approved biosimilar products. Two petitions asked the FDA to require labeling to make clear (such as through an agency statement that the product was not interchangeable) that a biosimilar product was not the same as a reference product,[482] while a third petition requested that the agency adopt a "same labeling" approach similar to that governing small-molecule brands and generics.[483] The FDA denied all three petitions in July 2016, reasoning that because it had is-

474. Food and Drug Administration Safety and Innovation Act ("FDASIA"), Pub. L. No. 112–144, § 1135, 126 Stat. 993, 1123 (2012).

475. The rule incorporated changes enacted by the FDASIA, in particular (1) shortening the FDA's required response period from 180 days to 150 days and (2) expanding the scope of 505(q) petitions to include biosimilar applications. 210 C.F.R. § 10 (2017); *see also* Eric Sagonowsky, *UPDATED: FDA's New Citizen Petition Rules Remove Speed Bumps for Generic, Biosimilar Approval*, FIERCEPHARMA (Nov. 9, 2016, 10:03 AM), http://www.fiercepharma.com/pharma/fda-changes-citizen-petition-rules-to-avoid-undue-generic-delays.

476. Novartis, Citizen Petition FDA-2013-P-1398 (filed Oct. 28, 2013), https://www.regulations.gov/document?D=FDA-2013-P-1398-0001.

477. *Id.*

478. Generic Pharm. Ass'n, Citizen Petition FDA-2013-P-1153 (filed Sept. 19, 2013), https://www.regulations.gov/document?D=FDA-2013-P-1153-0001.

479. Amgen Inc., Citizen Petition FDA-2014-P-1771 (filed Oct. 29, 2014), https://www.regulations.gov/document?D=FDA-2014-P-1771-0001.

480. Dept. of Health & Human Servs., Citizen Petition Denial Response FDA-2014-P-1771 (Mar. 25, 2015), https://www.regulations.gov/document?D=FDA-2014-P-1771-0004.

481. *Id.* at 4.

482. AbbVie, Citizen Petition FDA-2015-P-2000 (filed June 2, 2015), https://www.regulations.gov/document?D=FDA-2015-P-2000-0001; PhRMA & BIO, Citizen Petition FDA-2015-P-5022 (filed Dec. 15, 2015), https://www.regulations.gov/document?D=FDA-2015-P-5022-0001.

483. UAW Retiree Medical Benefits Trust, Citizen Petition FDA-2015-P-4529 (filed Nov. 24, 2015), https://www.regulations.gov/document?D=FDA-2015-P-4529-0001.

sued draft guidance only a few months earlier and had already received comments, the agency could consider the three petitions in the context of that guidance rather than as stand-alone petitions.[484]

One of the most far-reaching petitions challenged a central aspect of the biosimilar approval process. In April 2012, Abbott Laboratories,[485] sponsor of Humira, asked the FDA not to accept biosimilar applications referencing already approved biologic applications if the biosimilar was approved before March 23, 2010, the day the BPCIA became law.[486] The petition contended that if the FDA were to approve a biosimilar product on the basis that the referenced biologic was safe, pure, and potent, then the FDA would in effect be using a biologic's trade secrets—*i.e.*, its data and manufacturing information—to support its application.[487] Raising constitutional issues relating to Fifth Amendment takings, Abbott argued that the FDA should not use sponsors' applications submitted before the BPCIA's passage because those sponsors had no expectations that the FDA would be using their trade secrets.[488] The FDA ultimately denied the petition when it approved Amgen's Humira biosimilar Amjevita.[489]

Despite the lack of petitions filed by biologic manufacturers against biosimilar makers, there has been one 505(q) petition filed by a biosimilar manufacturer against another. Apotex filed a petition in May 2017 asking the FDA to require that all biosimilar applicants referencing Neulasta conduct comparative clinical efficacy studies in at least one patient population.[490] Five days later, another biosimilar maker, Coherus BioSciences, filed a comment in rebuttal, contending that FDA guidances require no such additional testing and that such studies would drain resources and reduce access to low-cost Neulasta biosimilars.[491] The FDA ultimately denied the petition, reasoning that a citizen petition was not the proper forum for the FDA to make "piecemeal" decisions re-

484. *See* Dept. of Health & Human Servs., Citizen Petition Denial Response, FDA-2015-P-4529, FDA-2015-P-2000, FDA-2015-P-5022 (filed July 12, 2016), https://www.regulations.gov/document?D=FDA-2015-P-4529-0012.

485. Abbott Laboratories has since spun off into two companies: Abbott and AbbVie, with AbbVie sponsoring Humira. *See* Jonathan D. Rockoff, *Abbott to Split Into Two Companies*, WALL ST. J. (Oct. 20, 2011), https://www.wsj.com/articles/SB10001424052970204853045766407408202887 66.

486. Abbott Labs., Citizen Petition FDA-2012-P-0317 (filed Apr. 2, 2012), https://www.regulations.gov/document?D=FDA-2012-P-0317-0001.

487. *Id.* at 2.

488. *Id.*; *see also* Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG. L.J. 285, 303 (2011).

489. Dept. of Health & Human Servs., Citizen Petition Denial Response from Abbott Labs. FDA-2012-P-0317 (filed Sept. 23, 2016), https://www.regulations.gov/document?D=FDA-2012-P-0317-0010. For a discussion of the issues raised in Abbott's petition, see Kurt R. Karst, *FDA Licenses First HUMIRA Biosimilar; Denies AbbVie Petition on Fifth Amendment Takings*, FDA LAW BLOG (Sept. 26, 2016), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2016/09/fda-licenses-first-humira-biosimilar-denies-abbvie-petition-on-fifth-amendment-takings.html.

490. Apotex, Inc., Citizen Petition FDA-2017-P-2803 (filed May 3, 2017), https://www.regulations.gov/docket?D=FDA-2017-P-2803.

491. Coherus BioSciences Inc., Comment on Apotex Citizen Petition FDA-2017-P-2803-0017 (filed May 9, 2017), https://www.regulations.gov/document?D=FDA-2017-P-2803-0017.

garding approvability outside the existing BPCIA framework.[492] A biosimilar's use of the process to raise the bar on other biosimilars calls for attention.[493]

We predict that in the biologics setting, the proportion of frivolous, anti-competitive 505(q) petitions will decrease while those raising legitimate scientific concerns will increase. For starters, and as discussed above,[494] biologics are complex and unpredictable, implicating legitimate safety and efficacy concerns. These characteristics are magnified because biosimilars will, at most, be similar (rather than identical) to the biologic.[495]

In addition, many biologic makers have also taken on the role of biosimilar manufacturers. Just to pick two examples, Pfizer markets the multi-billion-dollar drug Prevnar 13[496] (a BLA-approved vaccine that would face competition from a biosimilar), and also (after acquiring biosimilar maker Hospira) obtained biosimilar approval of Inflectra.[497] Similarly, Novartis has argued for a biosimilar-friendly naming rule[498] while also developing biologic products.[499] As noted above,[500] development costs are substantial, and thus only a subset of the pharmaceutical industry can develop these therapies. Because firms operate on both sides of the competitive ledger, some early movers in the biologics market may be hesitant to file petitions requesting heightened interchangeability or similarity testing because such arguments could be used against them when they act as a biosimilar. But as the first 505(q) petition shows, there is a chance that the stakes and benefits of marketing a biologic are so high that firms will take all possible steps to thwart follow-on competition, even if that results at times in the petitioner having to satisfy the same higher-approval standard for biosimilars it seeks to impose on others. At this time, it appears that manufacturers have taken a wait-and-see approach to petitions. Once the market has taken off and testing standards are clearer, however, 505(q) petitions could present a more tempting tactic to delay entry, as firms could rely on newly-issued approval guidelines and regulatory language to seek to delay competition.

In short, biologics so far have employed petitions not to delay biosimilar entry but to seek FDA guidance in clarifying labeling guidelines or raising concerns related to trade secrets. Because biosimilars implicate more nuanced immunogenicity, complexity, and related issues, there will be a greater need

492. Dept. of Health & Human Servs., Citizen Petition Denial Response FDA-2017-P-2803-0018 (Sept. 29, 2017), https://www.regulations.gov/document?D=FDA-2017-P-2803-0018.

493. Our prior study analyzing citizen petitions in the small-molecule context found that only 8% of 505(q) petitions were filed by nonbrand firms. Carrier & Minniti, *Citizen Petitions*, *supra* note 447, at 332.

494. *See supra* notes 32–52 and accompanying text.

495. *See supra* notes 51–52 and accompanying text.

496. *See* Cynthia Koons, *Pfizer Profit Tops Estimates as Prevnar Vaccine Sales Rise*, BLOOMBERG (Apr. 28, 2015, 6:10 AM), https://www.bloomberg.com/news/articles/2015-04-28/pfizer-cuts-2015-forecast-as-dollar-s-strength-cuts-into-sales.

497. Jonathan D. Rockoff, *Pfizer to Buy Hospira for $16 Billion*, WALL ST. J. (Feb. 5, 2015, 11:51 AM), https://www.wsj.com/articles/pfizer-to-buy-hospira-for-16-billion-1423138607.

498. *See supra* notes 476–77 and accompanying text.

499. Carolina Henriques, *Novartis Expands Immuno-oncology Pipeline and Testing Program*, IMMUNO-ONCOLOGY NEWS (Jan. 13, 2016), https://immuno-oncologynews.com/2016/01/13/novartis-continues-to-grow-immuno-oncology-pipeline-through-collaboration-and-licensing-agreement-with-surface-oncology/.

500. *See supra* note 62 and accompanying text.

for FDA guidance. Given the inherent purpose of citizen petitions—to give the public a voice in raising safety issues—we find it likely that petitions will play a prominent role in future biosimilar approval.

b. Assessment

The primary reason citizen petitions will increase, as shown in the previous Subsection, flows from biosimilars' complexity. This nuance and the nonidentical nature of biologics and biosimilars seem poised to increase the number of petitions and the likelihood they raise legitimate safety and effectiveness concerns. Petitions focusing on procedure, labeling guidelines, interchangeability, the patent dance, and trade secrets would be less likely to constitute sham petitions filed solely to delay biosimilar entry because they would be asking a government agency to clarify and interpret a new law.

As discussed above,[501] the *Noerr-Pennington* doctrine, which grants antitrust immunity to those petitioning the government, bears a well-recognized exception for sham petitions. Courts in the small-molecule setting have found that citizen petitions could be shams, with, for example, the court in *Louisiana Wholesale Drug Co. v. Aventis Pharmaceuticals* holding that a sham petition delayed generic entry[502] and the court in *Tyco Healthcare Group v. Mutual Pharmaceuticals* reversing summary judgment on a sham claim because the petition was "filed just one day after the district court granted [the generic] summary judgment of noninfringement—an event that results in lifting the automatic stay of the FDA's approval of the ANDA—and just one week before the end of the 30-month stay period."[503] In February 2017, the FTC, for the first time, filed an antitrust lawsuit challenging citizen petitions, claiming that Shire ViroPharma abused the regulatory process by filing 24 petitions and 19 additional FDA submissions within a 6-year period.[504]

In the biologics setting, the inherent complexity of the medicines and safety issues arising from follow-on products not identical to reference products will make it harder to prove that a petition is a sham. Petitions to date have focused on legal issues, and while they warrant close analysis given their potential to delay approval,[505] on the whole, they appear to present modestly less anticompetitive concern than in the small-molecule context.

Antitrust actions against petitions targeting biosimilars could also treat such conduct as one element in an overall scheme of monopolization. Courts have shown flexibility in evaluating an antitrust violation in the context of a

501. *See supra* notes 303–14 and accompanying text.

502. No. 07 Civ. 7343 (HB), 2008 WL 169362 (S.D.N.Y. Jan. 18, 2008).

503. 762 F.3d 1338, 1348 (Fed. Cir. 2014). For other cases that held that citizen petitions could be shams, see *In re* DDAVP Direct Purchaser Antitrust Litig., 585 F.3d 677, 694 (2d Cir. 2009); *In re* Prograf Antitrust Litig., No. 1:11-md-2242-RW2, 2012 WL 293850, at *6–7 (D. Mass. Feb. 1, 2012); *In re* Flonase Antitrust Litig., 795 F. Supp. 2d 300, 317 (E.D. Pa. 2011).

504. Federal Trade Commission v. Shire ViroPhama Inc., Complaint for Injunctive and Other Equitable Relief at ¶49, (No. 1:17-cv-00131-UNA) (D. Del. Feb. 7, 2017); *see Interview with FTC Commissioner Maureen Ohlhausen*, ANTITRUST SOURCE (Oct. 2012), https://www.ftc.gov/sites/default/files/documents/public_statements/interview-ftc-commissioner-maureen-ohlhausen/1210antitrustsource.pdf (highlighting FTC Chair Ohlhausen's "particular[] interest[] in the issues surrounding repetitive petitioning").

505. Carrier & Minniti, *Citizen Petitions*, *supra* note 447, at 307.

broader course of conduct,[506] and the combination of citizen petitions and other categories of behavior discussed in this Article could raise concern. Two examples from the small-molecule setting are Warner Chilcott's combination of petitions and product hopping to delay a generic acne medication[507] and Mylan's combination of petitions and settlements to delay a follow-on, allergic-reaction-treating EpiPen.[508]

F. Disparagement

While the conduct discussed in the first five sections of Part IV has been at the center of antitrust litigation, disparagement does not fall into that category. Given the nature of competition between brands and generics, there have been few antitrust cases challenging disparagement. Brands are not likely to falsely injure near-identical generics, which garner sales not from advertising campaigns but from state substitution laws.[509] In contrast, promotion, marketing, and the education of stakeholders will be crucial to the coming biosimilar wave,[510] which could implicate disparagement and require courts to address novel antitrust theories.

The Restatement of Torts explains that a party publishing "a false statement harmful to the interests of another" is liable for disparagement if the party (1) "intends for publication of the statement to result in harm" and (2) "knows that the statement is false or acts in reckless dis-regard of its truth or falsity."[511] The vast majority of courts have recognized that disparagement can give rise to a cognizable antitrust claim.[512] Such behavior can be uniquely effective in erecting barriers to competition, with one study finding that of "seven entry deterrence tactics identified, advertising was the most frequently employed tactic to deter entry of new products."[513]

In analyzing disparagement, courts have adopted one of three approaches. One group, led by the Third, Eighth, and D.C. Circuits, takes a case-by-case approach in assessing whether the alleged anticompetitive conduct violates the Sherman Act.[514] A second group, consisting of the Fifth and Seventh Circuits,

506. *See, e.g.*, *In re* Suboxone (Buprenorphine Hydrochloride & Naloxone) Antitrust Litig., No. 13-MD-2445, 2017 WL 36371, at *8 (E.D. Pa. Jan. 4, 2017); *In re* Gabapentin Patent Litig., 649 F. Supp. 2d 340, 359 (D.N.J. 2009); *In re* Neurontin Antitrust Litig., No. 02-1390, 2009 WL 2751029, at *15 (D.N.J. Aug. 28, 2009); Abbott Labs. v. Teva PharmUSA, Inc., 432 F. Supp. 2d 408, 428 (D. Del. 2006).

507. Carrier & Minniti, *Citizen Petitions*, *supra* note 447, at 347–49.

508. *Id.* at 350–51.

509. *See* Brad Weltman, *Why Pharmaceutical Advertising Is Virtually Absent from the Web*, ADWEEK (Nov. 2, 2016), http://www.adweek.com/news/advertising-branding/why-pharmaceutical-advertising-virtually-absent-web-174393.

510. Biosimilars Forum, *Awareness of Biosimilars Among U.S. Specialty Physicians Is High but New Survey Identifies Five Major Knowledge Gaps*, PR NEWSWIRE (Nov. 1, 2016), http://www.prnewswire.com/news-releases/awareness-of-biosimilars-among-us-specialty-physicians-is-high-but-new-survey-identifies-five-major-knowledge-gaps-300354609.html.

511. RESTATEMENT (SECOND) OF TORTS § 623A (AM. LAW INST. 1977).

512. *See* ABA SECTION OF ANTITRUST LAW, ANTITRUST LAW DEVELOPMENTS 301–03 (7th ed. 2012); Hillary Greene, *Muzzling Antitrust: Information Products, Innovation and Free Speech*, 95 B.U. L. REV 35, 45–46 n.50 (2015).

513. Maurice E. Stucke, *When A Monopolist Deceives*, 76 ANTITRUST L.J. 823, 839 n.75 (2010).

514. *See* W. Penn. Allegheny Health Sys., Inc. v. UPMC, 627 F.3d 85, 109 (3d Cir. 2010) ("[A]nticompetitive conduct can include . . . making false statements about a rival to potential investors and

reasons that false statements enhance competition in advertising markets, and thus that disparagement-based antitrust claims are not actionable.[515]

The third group, represented by the Second, Sixth, Ninth, Tenth, and Eleventh Circuits, offers the most frequently used approach. These courts apply a presumption that the exclusionary effects of disparagement are *de minimis*.[516] The plaintiff can rebut such a presumption only by showing that the alleged anticompetitive conduct is "[1] clearly false, [2] clearly material, [3] clearly likely to induce reasonable reliance, [4] made to buyers without knowledge of subject matter, [5] continued for prolonged periods, and [6] not readily susceptible of neutralization or other offsets by rivals."[517]

1. Small Molecules

Issues relating to disparagement have rarely arisen in the small-molecule setting given that the brands' and generics' active ingredient, form, dosage, strength, and safety and efficacy profile are the same[518] and that their rate and extent of absorption is largely equivalent.[519] Generics also do not need to promote or advertise their products because they can rely on state laws mandating or allowing automatic substitution.[520]

One rare example of a disparagement claim arising in connection with a follow-on drug occurred in the early days of the Hatch-Waxman Act. At the time the Act went into effect, brands took advantage of uncertainties in the transition to discourage pharmacists from prescribing generics. The case of *National Association of Pharmaceutical Manufacturers v. Ayerst Laboratories*[521] is instructive.

Beginning in 1967, Ayerst obtained approval for its product Inderal for multiple indications, including arrhythmia, hypertension, and angina.[522] In

customers," and "defamation, which plainly is not competition on the merits, can give rise to antitrust liability, especially when it is combined with other anticompetitive acts."); Caribbean Broad. Sys., Ltd. v. Cable & Wireless PLC, 148 F.3d 1080, 1087 (D.C. Cir. 1998) ("fraudulent misrepresentations" are "well within" the recognition that there are multiple forms of anticompetitive conduct); Int'l Travel Arrangers, Inc. v. W. Airlines, Inc., 623 F.2d 1255, 1267 (8th Cir. 1980) (deciding that a concerted campaign by an alleged monopolist involving newspaper advertisements, radio commercials, and a letter to customers were "a form of competition and because competition is the object sought to be preserved by the antitrust laws, we must be careful in drawing a line between fair competition, unfair competition, and competition that is so unfair as to rise to the level of an unreasonable restraint of trade").

515. *See* Retractable Tech., Inc. v. Becton Dickinson & Co., 842 F.3d 883, 895 (5th Cir. 2016) ("[A]bsent a demonstration that a competitor's false advertisements had the potential to eliminate, or did in fact eliminate, competition, an antitrust lawsuit will not lie."); Sanderson v. Culligan Int'l Co., 415 F.3d 620, 624 (7th Cir. 2005) ("Commercial speech is not actionable under the antitrust laws.").

516. *See* Duty Free Am.'s, Inc. v. Estee Lauder Cos., 797 F.3d 1248, 1268–69 (11th Cir. 2015); Lenox MacLaren Surgical Corp.v. Medtronic, Inc., 762 F.3d 1114, 1127–28 (10th Cir. 2014); Am. Council of Certified Podiatric Physicians & Surgeons v. Am. Bd. of Podiatric Surgery, Inc., 323 F.3d 366, 370 (6th Cir. 2003); Am. Prof'l Testing Serv., Inc. v. Harcourt Brace Jovanovich Legal & Prof'l Publ'ns, Inc., 108 F.3d 1147, 1152 (9th Cir. 1997); Nat'l Ass'n of Pharm. Mfrs., Inc. v. Ayerst Labs., Div. of/& Am. Home Prod. Corp., 850 F.2d 904, 916 (2d Cir. 1988).

517. *Nat'l Ass'n of Pharm. Mfrs., Inc.*, 850 F.2d at 916.

518. *See supra* note 83 and accompanying text.

519. *Id.*

520. Carrier, *A Real-World Analysis*, *supra* note 112, at 1017; MASSON & STEINER, *supra* note 114.

521. 850 F.2d 904.

522. *Id.* at 907.

1983, it received approval for treatment after heart attacks.[523] One year later, Congress passed the Hatch-Waxman Act, which included a provision that drugs approved between 1982 and 1984 would gain exclusivity until 1986.[524] As a result, approved generic versions of Inderal could not be marketed for post-heart-attack treatment until that time.[525]

In October 1985, generics sent a letter to California pharmacists explaining that their versions were "therapeutically equivalent" and could be dispensed "without fear."[526] Ayerst responded by writing a letter to the same pharmacists warning that "[t]he issue of possible liability associated with dispensing a generic drug for an indication not included in its labeling has not been resolved in the courts" and that it is "not possible to determine, in advance, the outcome of a suit which may arise from such a situation."[527] The warnings continued: "[i]t is clear, however, that litigation is troublesome, expensive and will generate adverse publicity," and that even if generics offered indemnification, "no company could adequately compensate you for the trouble and negative publicity that may result from a court case."[528] Ayerst concluded by asserting that "consistent with prudent pharmacy practice, you will want to dispense INDERAL tablets, the only propranolol product with the approved indication for reduction of mortality post-[heart attack]."[529]

Generics responded to Ayerst's letter by suing for attempted monopolization.[530] The court explained that "[a]dvertising that emphasizes a product's strengths and minimizes its weaknesses does not, at least unless it amounts to deception, constitute anticompetitive conduct" violating Section 2.[531] As a result, a plaintiff must "overcome a presumption that the effect on competition of such a practice was *de minimis*."[532] The court applied a framework offered in the leading antitrust treatise, which stated:

> [A] plaintiff may overcome the de minimis presumption "by cumulative proof that the representations were [1] clearly false, [2] clearly material, [3] clearly likely to induce reasonable reliance, [4] made to buyers without knowledge of the subject matter, [5] continued for prolonged periods, and [6] not readily susceptible of neutralization or other offset by rivals."[533]

The court ultimately overturned the lower court's dismissal on the grounds that the FDA informed Ayerst that the letter was "false and misleading" and an "at-

523. *Id.*
524. *Id.*
525. *Id.*
526. *Id.*
527. *Id.* at 908.
528. *Id.*
529. *Id.*
530. *Id.*
531. *Id.* at 916.
532. *Id.* (quoting Berkey Photo, Inc. v. Eastman Kodak Co., 603 F.2d 263, 288 n.4 (2d Cir. 1979)).
533. *Id.* (quoting 3 P. Areeda & D. Turner, *Antitrust Law* ¶ 738a, at 279 (1978).

tempt to intimidate pharmacists," and that it could have demonstrated exclusionary conduct.[534]

Two other examples of disparagement claims arising in the small-molecule context arose in *In re Suboxone* and *In re Warfarin Sodium*. First, in *Suboxone*,[535] Reckitt Benckiser, manufacturer of the billion-dollar, opioid-addiction-treating Suboxone, faced a claim that it had engaged in a systematic effort to switch the market from a tablet to a sublingual (under-the-tongue) film.[536] After obtaining FDA approval to market this film, Reckitt allegedly "disparaged Suboxone tablets and warned of false safety concerns."[537] Plaintiffs claimed that Suboxone sales representatives "met with physicians to promote the film formulation while simultaneously discouraging [them] from writing prescriptions for Suboxone tablets under the guise of false safety concerns—in particular, that the lack of unit dose packaging in the tablets raised the risk of pediatric exposure."[538] But instead of removing the product, Reckitt continued to sell tablets, which plaintiffs argued "demonstrate[d] the falsity of Reckitt's stated safety concerns."[539] The court found that the allegations were "made with particularity" and were sufficient to "place the defendants on notice."[540]

Finally, in *Warfarin Sodium*, generics asserted that DuPont, sponsor of the blockbuster blood thinner Coumadin, had published false and misleading statements concerning the bioequivalence, therapeutic efficacy, and safety of generic Coumadin.[541] Among other things, DuPont "repeatedly claimed in press releases and promotional brochures targeted at doctors that additional blood tests and monitoring had to be done when interchanging Coumadin with a generic substitute."[542] Likewise, patients and 45,000 different pharmacists were directed to call an "800" telephone number in response to full-page newspaper advertisements.[543] Even more concerning, a DuPont "press release issued within days after [the generic was introduced] implied that the cheaper generic substitute sacrificed patient safety to focus on cost."[544]

This conduct compelled the FDA to send out a notice rebutting DuPont's false and misleading communications.[545] As a result of its conduct, DuPont maintained 75% market share after one year and "some pharmacies, including large chains, refused to substitute the generic for Coumadin out of a mistaken belief that generic warfarin sodium was not equivalent to Coumadin."[546] DuPont ultimately settled the antitrust suit before the Third Circuit issued a substantive ruling on the anticompetitive nature of the alleged disparagement,

534. *Id.* at 908, 916, 917.
535. *In re* Suboxone Antitrust Litig., 64 F. Supp. 3d 665 (E.D. Pa. 2014).
536. *Id.* at 679.
537. *Id.* at 674.
538. *Id.* at 683.
539. *Id.*
540. *Id.*
541. *See In re* Warfarin Sodium Antitrust Litig., 212 F.R.D. 231, 241 (D. Del. 2002).
542. *Id.*
543. *Id.*
544. *Id.*
545. *Id.* at 255–56.
546. *Id.* at 242.

but the court asserted that the "facts as alleged in the complaints plainly establish the required causal connection between DuPont's exclusionary anticompetitive conduct and the direct harm to Coumadin purchasers."[547]

2. Biologics

To an extent not seen in the small-molecule setting, biologics will present disparagement issues. And when they do, courts will confront nuanced antitrust analysis.

a. Likelihood

Unlike the relationship between brands and generics, competition between biologics and biosimilars will require marketing and advertising to differentiate products, which increases the likelihood of disparagement. In the small-molecule setting, the products are nearly identical, which reduces the need for brand advertising campaigns against generics. This effect is compounded as generics are selected through substitution laws, rather than patient- or physician-purchasing habits. As one commentator put it, biosimilars "are a version of an existing biologic but because of the nature of specialty drugs will act as a brand in many ways," which will require promotion that is "accompanied by an overarching educational message."[548]

With increased head-to-head advertising battles comes the possibility of disparagement claims. Biologic manufacturers, as in *Ayerst* and *Warfarin Sodium*, may seek to influence, or even intimidate, prescribers by exaggerating the differences with biosimilars and highlighting potential tort liability,[549] and sales representatives could communicate false information against biosimilars. Given the expected increase in comparative advertising efforts between similar (though not identical) products battling for market share, we anticipate an increased frequency of anticompetitive disparagement claims.

b. Assessment

A disparagement claim would likely assert that a biologic's misrepresentation about the biosimilar would reduce demand, allowing the biologic manufacturer to increase its market power, as occurred in the *Warfarin Sodium* case.[550] As discussed above,[551] the two most common judicial approaches (1) require plaintiffs to overcome a presumption that false statements about ri-

547. *See In re* Warfarin Sodium Antitrust Litig., 391 F.3d 516, 522 (3d Cir. 2004); *In re* Warfarin Sodium Antitrust Litig., 214 F.3d 395, 402 (3d Cir. 2002).

548. NIAZI, *supra* note 21, at 360.

549. *See* Jessica Benson Cox et al., *Biologics, Biosimilars, Bioequivalents—Oh My! Product Liability Considerations for Biologics and Biosimilars*, FOR DEFENSE, Sept. 2015, at 31 (discussing how an increase in manufacturing defect claims "may open biologic manufacturers up to increasing liability in certain jurisdictions").

550. Another type of conduct is false advertisement, by which a monopolist's false affirmations about itself have the potential to reduce competition with others. *See* Stearns Airport Equipment Co. v. FMC Corp., 170 F.3d 518 (5th Cir. 1999).

551. *See supra* notes 532–33 and accompanying text.

vals have a *de minimis* effect on competition[552] and (2) apply a case-by-case framework.[553]

First, a case from the medical device industry, *Lenox MacLaren Surgical v. Medtronic*,[554] provides a guidepost for analysis based on the *de minimis* approach. In that case, Lenox, a manufacturer of bone mills used in spinal-fusion surgery, entered into an agreement by which Medtronic was to distribute the product to hospitals.[555] After the agreement broke down, Lenox alleged that Medtronic engaged in disparagement that constituted monopolization by telling potential customers that its device was dangerous and helping to initiate a recall.[556] Applying the six-factor test,[557] the Tenth Circuit found that Lenox offered evidence to rebut the presumption of a *de minimis* impact on competition.[558]

The court's discussion of three of the six factors is instructive.[559] For the fourth factor—whether the alleged statement was made to buyers without knowledge of the subject matter—the court found that "even sophisticated consumers [like hospitals and group purchasing organizations] would rely on Medtronic's false statements."[560] For the fifth factor, the court found that the continued listing of Lenox's device on the FDA's website as recalled was enough to show a prolonged period.[561] And the court found the sixth factor—whether the plaintiff could show that it could not readily neutralize the disparaging statement—satisfied from "worries involving malpractice liability," which resulted in "hospitals [being] unwilling to purchase" recalled products.[562]

At its core, the *Lenox* court emphasized the effect of potential liability concerns in secondary markets. Just as the *Lenox* purchasers were concerned with liability, the central issue confronting doctors' future use of biosimilars involves whether they are convinced the product operates in a similar manner to the biologic or instead threatens safety or efficacy. Lenox provides a useful guidepost to future courts in emphasizing liability concerns as a factor that can overcome the presumption of a *de minimis* impact on competition.

552. *See* Lenox MacLaren Surgical Corp. v. Medtronic, Inc., 762 F.3d 1114, 1127 (10th Cir. 2014); Am. Council of Certified Podiatric Physicians & Surgeons v. Am. Bd. of Podiatric Surgery, Inc., 323 F.3d 366, 370 (6th Cir. 2003); Am. Prof'l Testing Serv., Inc. v. Harcourt Brace Jovanovich Legal & Prof'l Publ'ns, Inc., 108 F.3d 1147, 1152 (9th Cir. 1997); Nat'l Ass'n of Pharm. Mfrs. v. Ayerst Labs., 850 F.2d 904, 916 (2d Cir. 1988).

553. As noted above, another approach, adopted by the Fifth and Seventh Circuits, essentially bars antitrust claims based on disparagement on the basis that such conduct is procompetitive and merely offers competition in the advertising market. *See supra* note 515. *But see* Stucke, *supra* note 513, at 825 ("Deception lacks any redeeming economic qualities or cognizable efficiency justifications.").

554. 762 F.3d 1114 (10th Cir. 2014).

555. *Id.* at 1116.

556. *Id.* at 1126–27.

557. *See* Nat'l Ass'n of Pharm. Mfrs., Inc. v. Ayerst Labs., 850 F.2d 904, 916 (2d Cir. 1988).

558. 762 F.3d at 1128.

559. For the first three factors, the district court adopted the findings of an arbitration panel that had found that the conduct was false, was material, and induced reliance. Lenox MacLaren Surgical Corp. v. Medtronic, Inc., 2013 WL 3179204, at *18 (D. Colo. June 21, 2013), *rev'd*, 762 F.3d 1114 (10th Cir. 2014).

560. 762 F.3d at 1127.

561. *Id.*

562. *Id.*

The second framework courts could apply would rely on case-by-case analysis. Courts applying this approach have appreciated that anticompetitive conduct takes "too many different forms, and is too dependent upon context, for any court or commentator ever to have enumerated all the varieties."[563] Under this approach, one relevant factor is the role disparagement plays in a biosimilar's ability to finance already-high expenses. In *West Penn Allegheny*, for example, the Third Circuit determined that false statements to investors about a competitor's financial health caused the rival to pay inflated financing costs on its debt and demonstrated anticompetitive conduct sufficient to survive a motion to dismiss.[564]

A second factor that courts have analyzed under the case-by-case approach is the extent to which false statements lock in physician decision-making. In *United States v. Microsoft*, for example, the D.C. Circuit found that deceptive statements to Java-based software developers about the interoperability of Windows-based systems with other platforms resulted in the development of software compatible only with Windows and demonstrated anticompetitive conduct violating Section 2.[565] By analyzing conduct as a whole, without requiring a showing exceeding *de minimis* harm, the case-by-case approach offers more flexibility for biosimilar manufacturers bringing disparagement claims.

More than any other category, disparagement will present challenges that have not been confronted in the small-molecule setting. Analysis should consider the science and markets of biologics and biosimilars and significant competitive effects of false statements. Taking the *Ayerst*, *Lenox*, *Suboxone*, *Warfarin Sodium*, and other cases as guides, courts can determine whether plaintiffs' disparagement claims constitute monopolization.

G. Collusion

In contrast to many of the topics discussed in this Article, little nuance is required in the antitrust analysis of price collusion. Because of its severe anticompetitive effects, difficulty of discernment, and lack of procompetitive justifications, such conduct is treated as a *per se*, or automatic, violation of the antitrust laws.[566] The main challenge in collusion cases involves marshaling evidence that the conduct occurred, with a showing of parallel price increases generally not sufficient.[567] Once that evidence is shown, the collusion case is straightforward.

563. W. Penn. Allegheny Health Sys., Inc. v. UPMC, 627 F.3d 85, 109 (3d Cir. 2010); Caribbean Broad. Sys., Ltd. v. Cable & Wireless PLC, 148 F.3d 1080, 1087 (D.C. Cir. 1998).

564. *W. Penn. Allegheny*, 627 F.3d at 109–10.

565. 253 F.3d 34, 76–77 (D.C. Cir. 2001).

566. United States v. Socony-Vacuum Co., 310 U.S. 150 (1940).

567. *E.g.*, *In re* Musical Instruments & Equip. Antitrust Litig., 798 F.3d 1186, 1197 (9th Cir. 2015).

1. Small Molecules

Typical pharmaceutical antitrust cases in the small-molecule setting have challenged the array of conduct mentioned throughout this Article. In contrast, there have been few collusion cases. One significant development occurred in late 2016 when 20 (eventually expanding to 41) state Attorneys General sued Teva, Mylan, and four other generics, asserting a "broad, well-coordinated, and long-running series of schemes to fix the prices and allocate markets" for antibiotic Doxy DR and diabetes-treating Glyburide.[568]

The states alleged that the "anticompetitive schemes" were carried out in two ways.[569] First, "to avoid competing with one another and thus eroding the prices for certain drugs," defendants "communicated with each other to determine and agree on how much market share or which customers each competitor was entitled to."[570] The defendants then "effectuated the agreement by either refusing to bid for particular customers or by providing a cover bid that they knew would not be successful."[571] The second means involved "simply communicat[ing]—typically either in person, by telephone, or by text message—and agree[ing] to collectively raise prices for a particular generic drug."[572] The case reveals a typical collusion scenario involving rivals conspiring to evade the operation of competitive markets by fixing price and other elements of competition.

2. Biologics

Although some characteristics of biologics reduce the likelihood of collusion, more potent effects, including the private exchange of information in the patent dance, increase its frequency. Once collusion is shown, the antitrust analysis should be just as rigorous as in the small-molecule setting.

a. Likelihood

The challenges of successfully engaging in collusion ensure that it will not be common. But compared to the small-molecule setting, characteristics of the biologics market point in the direction of increased collusion. The likelihood of collusion is higher because of (1) the smaller number of biologics and biosimilars, which makes it easier to coordinate,[573] (2) an inelastic demand for the products because consumers lack effective substitutes,[574] and (3) a more

568. Connecticut v. Aurobindo Pharma USA, Inc., No. 3:16-cv-02056 (complaint filed Dec. 15, 2016). The Department of Justice is also investigating generic price fixing. *See* Katie Thomas, *20 States Accuse Generic Drug Companies of Price Fixing*, N.Y. TIMES, Dec. 16, 2016, at B2.

569. Complaint at 4, Connecticut v. Aurobindo Pharma USA, Inc., No. 3:16-cv-02056 (D. Conn. filed Dec. 15, 2016).

570. *Id.* at 4–5.

571. *Id.*

572. *Id.* at 5.

573. *See supra* note 79 and accompanying text.

574. *See supra* notes 50–52 and accompanying text.

private negotiation process between the parties.[575] On the other hand, the heterogeneity of the products makes it more difficult to coordinate on price.[576] In other words, the nonidentical nature of the products, together with the absence of widespread automatic substitution laws, means that different submarkets may blossom—for example, with certain insurance providers granting higher reimbursements for biosimilars within the same category—making it harder to fix prices.[577]

The private nature of the patent dance increases the likelihood of collusion. In contrast to the public Orange-Book listing of patents under the Hatch-Waxman Act, the patent dance at the heart of litigation between biologics and biosimilars is a private affair, with no obligation to publicize the substance of any settlement. As a result, the two sides could use this lack of transparency to coordinate, benefiting both parties while harming other biosimilars or the public at large.

For example, a biologic manufacturer could convince a biosimilar maker to avoid including weaker Paragraph 3 (initial-list) patents[578] in its Paragraph 5 (simultaneous-exchange) list "in exchange for a promise not to bring suit against a future product."[579] Not only would the biosimilar benefit from such a promise, but it also would help the biologic, which "collude[s] to litigate only a portion of the patents that could be litigated," thereby hiding patents to "prevent future design-around attempts by other follow-on manufacturers or to prevent the follow-on manufacturer from invalidating weak patents."[580] Prices would remain high as the biologic allows the approval of one biosimilar while blocking others through infringement claims.[581] Adding insult to injury, the BPCIA's "list it or lose it" provisions would be undermined because a patent that should have been included on a Paragraph 3 list[582] could be circumvented through collusive actions.[583] In short, the private nature of the process together

575. *See, e.g.*, *In re* Plasma-Derivative Protein Therapies Antitrust Litig., 764 F. Supp. 2d 991, 1002 (N.D. Ill. 2011).

576. *E.g.*, Dean Harvey, *Anticompetitive Social Norms as Antitrust Violations*, 94 CALIF. L. REV. 769, 776 (2006).

577. In addition to the relationship between biologics and biosimilars, two other forms of collusion are conceivable. First, two biologics manufacturers could collude. But this would not appear to be likely since each product would represent its own market, making it more difficult to coordinate across disparate fundamental characteristics. *See supra* notes 379–80 and accompanying text. Second, biosimilars could collude with each other but this also would be less likely than in the small-molecule setting because biosimilar sales are not a function of automatic substitution laws, thus avoiding government-mandated dispersal of low-cost alternatives. *See* Irena Royzman, *The Value of Being Highly Similar: First U.S. Biosimilar*, BNA LIFE SCI. L. & INDUSTRY REP., Apr. 17, 2015, https://www.pbwt.com/content/uploads/2015/07/Bloomberg-BNA-The-Value-of-Being-Highly-Similar-First-US-Biosimilar.pdf (explaining that biologic competitors are already competing on Medicare reimbursement rates, which disincentivizes collusion for the successful company). The higher safety or efficacy of one biosimilar could call for a price premium, with differences in the premium's valuation making agreement more difficult.

578. 42 U.S.C. § 262(l)(3) (2012).

579. Charles Davis, *Take Two and Call Congress in the Morning*, 81 GEO. WASH. L. REV. 1255, 1282 (2013).

580. *Id.* at 1282–83.

581. *Id.* at 1283.

582. 35 U.S.C. § 271(e)(6)(C) (2012) ("owner of a patent that should have been included" in initial patent list or under newly issued or licensed patent provision "but was not timely included in such list . . . may not bring an action under this section for infringement of the patent with respect to the biological product").

583. Davis, *supra* note 579, at 1283.

with the more limited universe of players and inelastic demand would appear to outweigh the more heterogeneous nature of the products in increasing the likelihood of collusion.

Given the likelihood of collusion, Congress could require biologics and biosimilars to file settlements with the FTC. The 2003 Medicare Amendments[584] required such filings in the small-molecule setting, which has resulted in the FTC becoming aware of all drug patent settlements and filing annual reports on the behavior.[585] Because it lacks such a provision, the BPCIA allows parties to settle patent litigation without worrying that the government agencies will review (or even be aware of) the settlement.[586] An easy way to address this blind spot is to amend the BPCIA to require settling parties to provide their agreement to the antitrust agencies within 10 days of the settlement.

b. Assessment

While the frequency of collusion is unclear, the antitrust assessment is not. Just as price fixing, market division, and similar collusive behavior have long constituted *per se* violations of the antitrust laws in the small-molecule and other contexts,[587] the same analysis should apply in the setting of biologics and biosimilars. Collusion similar to that hypothesized in the patent dance setting threatens higher prices, reduced follow-on competition, and an evasion of the regulatory regime. Given the private nature of collusion in general, and aspects of the patent dance in particular, the greatest challenge will be uncovering such collusion. But if such evidence is shown, antitrust liability is clear.

* * *

Part IV has offered a tour of the seven most important types of behavior in pharmaceutical antitrust law. Exploring the differences in the regimes, like the private nature of notice and litigation in biologics, it has highlighted concerns from submarine patents and shell licensing. And it has uncovered distinctions in the science that support conclusions on the frequency of product hopping and citizen petitions. This Part has concluded that disparagement, citizen petitions, collusion, and (at least in the short term) regulatory abuse will increase and that product hopping and reverse-payment settlements will decrease. Relatedly, it has encouraged robust antitrust analysis of each of the types of conduct and modestly more deferential antitrust scrutiny of citizen petitions.

584. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108–173, 117 Stat. 2066 (codified as amended in scattered sections of 21, 26, and 42 U.S.C.); *see also* 146 CONG. REC. E1538 (daily ed. Sept. 20, 2000) (statement of Rep. Waxman) (legislation sought to prohibit "secret, anticompetitive agreements").

585. Press Release, Fed. Trade Comm'n, FTC Staff Issues FY 2015 Report on Branded Drug Firms' Patent Settlements with Generic Competitors (Nov. 1, 2017), https://www.ftc.gov/news-events/press-releases/2017/11/ftc-staff-issues-fy-2015-report-branded-drug-firms-patent (noting that, while total number of settlements increased, potential pay-for-delay settlements fell between 2012 and 2015 from 40 to 14).

586. *See* Statement of Lee Purvis, at 60, https://www.ftc.gov/system/files/documents/public_events/171301/140204biologicstranscript.pdf; *see also* Davis, *supra* note 579, at 1290.

587. U.S. DEP'T OF JUSTICE ANTITRUST DIV., AN ANTITRUST PRIMER FOR FEDERAL LAW ENFORCEMENT PERSONNEL 4–11 (rev. 2005).

V. CONCLUSION

We stand poised at the precipice of an industry worth hundreds of billions of dollars that has already begun to treat cancer and other serious conditions. This Article has analyzed the frequency with which competition issues are likely to arise and has offered an antitrust assessment of the most likely forms of anticompetitive behavior.

More than any other industry, pharmaceuticals offer a meticulously calibrated regime balancing competition and innovation. The need to incentivize novel, life-saving medicines is critical. But so is the ability to provide such treatments in an affordable manner. And while aspects of the pharmaceutical regime have proved successful, the complexities, combined with the effects of follow-on entry, tempt companies to circumvent the framework.

Learning the lessons from the small-molecule setting makes it more likely that the goals of the biologics regime will be effectuated. Before Congress's goals are undermined, this project sounds the alarm bells of regime-threatening conduct like submarine patents, shell licensing, reverse-payment settlements, disparagement, sample denials, and collusion. At the same time, it learns from the industry's science and markets that complexity justifies many citizen petitions and makes product hopping and settlements less likely.

In looking forward to the new biologics landscape, a look backward to the lessons learned from the small-molecule setting offers significant benefits for competition, innovation, and an appropriate implementation of the new regime. With biosimilar entry poised to be unleashed in crucial multi-billion-dollar markets, there is no time to waste.